SECOND SERIES FEBRUARY 1938 VOL. 14, NO. 2

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

CONTENTS

The Nature of Glomerulonephritis 53
George Baehr

Clinical Aspects of Nephritis 65
Robert F. Loeb

Calculous Disease in the Urinary Tract 76
Linwood D. Keyser

Recent Accessions to the Library 98

Proceedings of Academy Meetings 100

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

Published monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York

Entered as second-class matter, February 3, 1928, at the Post Office at New York, N. Y., under the Act of August 24, 1912. Subscription $2.00 per year. Single copies, 25 cents

OFFICERS AND STAFF OF THE ACADEMY

1938

President

JAMES ALEXANDER MILLER

Vice-Presidents

HARRY ARANOW
ARTHUR F. CHACE
BENJAMIN P. WATSON

Treasurer

BERNARD SACHS

Assistant Treasurer

RODERICK V. GRACE

Recording Secretary

LEWIS F. FRISSELL

Trustees

SAMUEL W. LAMBERT — GEORGE BAEHR — WALTER L. NILES
CHARLES F. TENNEY — FREDERICK TILNEY — EUGENE H. POOL
WILLIAM S. LADD — WALTER W. PALMER — FREDERIC E. SONDERN
HERBERT B. WILCOX

Council

The President
The Vice-Presidents — The Trustees — The Treasurer
The Recording Secretary
The Chairmen of Standing Committees

Director

JOHN A. HARTWELL

Librarian

ARCHIBALD MALLOCH

Executive Secretary
Committee on Medical Education

MAHLON ASHFORD

Executive Secretary
Public Health Relations Committee

E. H. L. CORWIN

Executive Secretary
Medical Information Bureau

IAGO GALDSTON

Library Consultants

LAURA E. SMITH — B. W. WEINBERGER — ARNOLD C. KLEBS

Legal Counsel

FRANK L. POLK, ESQ.

EDITORIAL BOARD

JEROME P. WEBSTER, *Chairman*
EUGENE F. DUBOIS
ROBERT F. LOEB
ALFRED E. COHN
H. BURTON LOGIE
ARCHIBALD MALLOCH
KARL VOGEL
MAHLON ASHFORD, *Secretary & Editor*

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

FEBRUARY 1938

THE NATURE OF GLOMERULONEPHRITIS*

GEORGE BAEHR

Associate in Pathology and Attending Physician, The Mount Sinai Hospital

IT HAS become necessary to redefine glomerulonephritis, for old misconceptions have been revived in several recent pathological and clinical publications so that the subject is again in danger of being enveloped in the confusion which existed up to twenty-five years ago. The fault lies with some of our pathologists who lay undue weight upon cellular morphology and too little upon the whole picture of the disease. They exaggerate the significance of nonspecific cellular changes commonly seen postmortem in some of the renal glomeruli and regard them as lesser degrees of glomerulonephritis. This misinterpretation of a common postmortem finding is analogous to the clinical error of diagnosing glomerulonephritis merely because of the presence of albumin and casts or of red blood cells in the urine.

By fixing kidneys in Helly's or Zenker's fluid and staining with the Mallory-Heidenhain azocarmine method, Bell[1] has demonstrated a minor degree of swelling of glomerular endothelium in many kidneys. It occurs at death in a variety of infections as well as in noninfectious diseases and, except in rare instances, is not associated with clinical manifestations of glomerulonephritis during life. Without clinical justification, he chooses

* Delivered November 3, 1937 in the Tenth Annual Graduate Fortnight

to call these glomerular changes "subclinical glomerulitis" and sees "transitions between this subclinical glomerulitis and acute glomerulonephritis." (Fig. 1 A).

In other words, Bell conceives of glomerulonephritis as merely the advanced stage of glomerular changes which occur very commonly at death in varying diseases in which acute glomerulonephritis almost never occurs. Thus, he finds it in 41 per cent of cases of acute rheumatic endocarditis, a disease in which true glomerulonephritis is peculiarly rare.[2] In subacute bacterial endocarditis, he finds it in 79 per cent of the cases, although the absence of acute glomerulonephritis is a peculiar characteristic of the bacterial stage of this disease in contrast to bacteria-free cases.[3] Bell also describes it in 52.4 per cent of patients dying of puerperal sepsis, in 39.7 per cent of cases of pulmonary tuberculosis, in 50 per cent of lobar pneumonias and in 37.5 per cent of a miscellaneous variety of infections such as typhoid fever, septicemia, appendicitis, meningitis, diphtheria. He finds it in primary arterial hypertension, old healed valvular heart disease, pernicious anemia (four out of seven cases), carcinoma, subacute yellow atrophy of the liver. True clinical glomerulonephritis is observed so rarely during the course of these diseases that its occurrence may be regarded as an accidental coincidence. There is therefore no reason to believe that these very common minor glomerular changes bear any relationship to glomerulonephritis.

The unacceptable premise that these common glomerular alterations are a less intense variety of acute glomerulonephritis, leads Bell to an erroneous conclusion, "that acute glomerulonephritis is not a sharply circumscribed entity." It is the purpose of this paper to review some clinical and pathological experiences which demonstrate

(1) that acute glomerulonephritis (acute Bright's disease) is a sharply circumscribed entity,

(2) that it is part of a disease of the body as a whole,

(3) that its clinical manifestations can be related to characteristic pathological phenomena in various parts of the body,

(4) that the disease has a specific etiology and pathogenesis.

The Acute Onset.—It is often insufficiently appreciated that acute diffuse glomerulonephritis *always* has an extraordinarily sudden onset. The disease actually begins with explosive suddenness. The glomeruli seem to be damaged simultaneously. In patients who die within a few weeks after the onset, all the glomerular lesions are in the identical stage

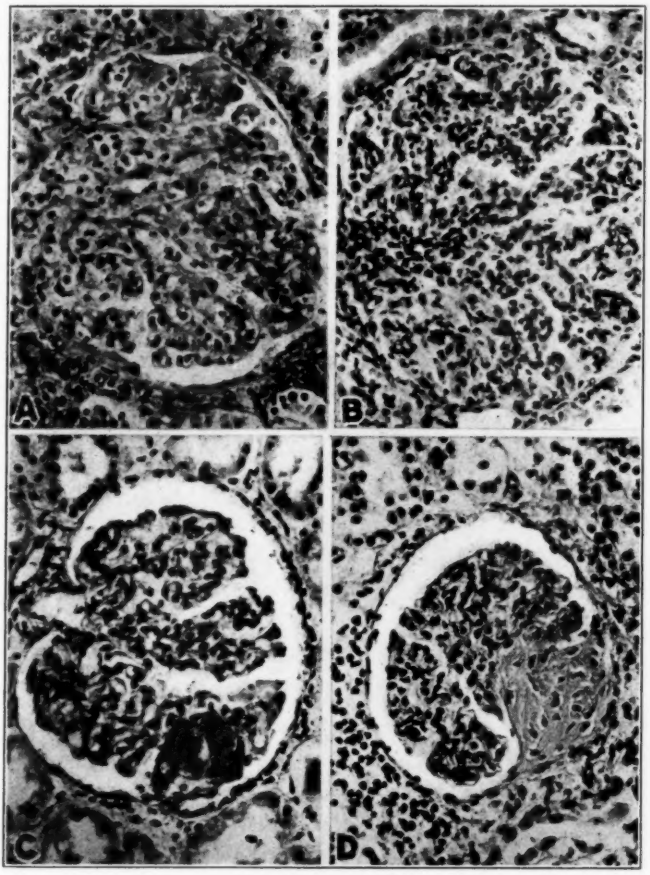


Fig. 1 A, B, C, D

A. Glomerular changes in acute bacterial (pneumococcus) endocarditis (Bell's glomerulitis). A common postmortem finding in many diseases, infectious, as well as non-infectious. Lesion in this case is probably due to direct action of bacteria or their toxins. Endothelial swelling of glomerular capillaries resembles glomerulonephritis, but the glomerular capillaries contain blood, the swelling affects only some of the glomeruli and the process is pathogenetically and clinically unrelated to true glomerulonephritis.

B. Typical glomerular lesion in acute diffuse glomerulonephritis. Swelling and proliferation of glomerular endothelium, obliteration of Bowman's capsular space by maximum glomerular swelling, bloodless capillary loops, beginning necrosis of loops. The process has affected all glomeruli throughout the kidney simultaneously.

C. Fresh embolic glomerular lesion in subacute bacterial (Streptococcus viridans) endocarditis. The unaffected glomerular capillaries are normal anatomically and functionally.

D. Old healed embolic glomerular lesion in subacute bacterial endocarditis. Only healed embolic lesions are found in cases which have become bacteria-free. In active cases with positive blood cultures and bacterial colonies in the vegetations, all stages of the process are usually to be seen from freshly embolized loops to completely healed lesions.

of development, although perhaps of varying severity (Fig. 1 B).

This is in sharp contrast with focal glomerulonephritis or the embolic glomerular lesions of subacute bacterial endocarditis (Loehlein[4], Baehr[5]). Embolic glomerular lesions recur in repeated showers over a period of months or even years. In patients who die during the bacterial stage of subacute bacterial endocarditis, all stages of glomerular damage can be recognized from the fresh necrosis of glomerular loops, embolized within a few days, to old completely organized glomerular segments (Fig. 1 C and D). Even in massive glomerular embolizations, many normal glomeruli can still be seen as well as normal portions of affected glomeruli. For this reason, the embolic glomerular lesions of subacute bacterial endocarditis, unlike acute diffuse glomerulonephritis, rarely, if ever, cause disturbances in renal function and are therefore of little clinical significance[6].

In a condition which I have called benign hemorrhagic nephritis[7], renal damage induced by remote foci of chronic infection such as diseased tonsils, results either in persistent or recurring hematuria. The nature of the lesion is unknown because the patients do not die of their renal disease. The bilateral hematuria is probably due to repeated rupture of damaged glomerular capillaries. Although the hematuria may persist for months, the circulation through the glomerular capillaries remains unimpaired, for the condition never gives rise to hypertension, edema or to disturbances in renal function.

A Disease of the Body as a Whole.—Clinically as well as pathologically, acute glomerulonephritis is part of a diffuse systemic disturbance which affects the capillaries and finer ramifications of the vascular apparatus of the entire body. Acute Bright's disease can be suspected clinically if albumin, casts and red blood cells appear suddenly in a previously normal urine during recovery from a streptococcus infection. An early diagnosis can only be made positively, if in addition to the urinary findings there are clinical evidences of extrarenal vascular damage such as arterial hypertension, transient edema of the eyelids, face or body or clinical evidences of vascular disturbances in the skin, the brain, the ocular fundus or the myocardium.

Disturbances of the myocardium may occur with the very onset of the disease and are common during the first weeks. There is often tachycardia, arrhythmias, precordial discomfort. The electrocardiogram is apt to show varying transient abnormalities from day to day, including T

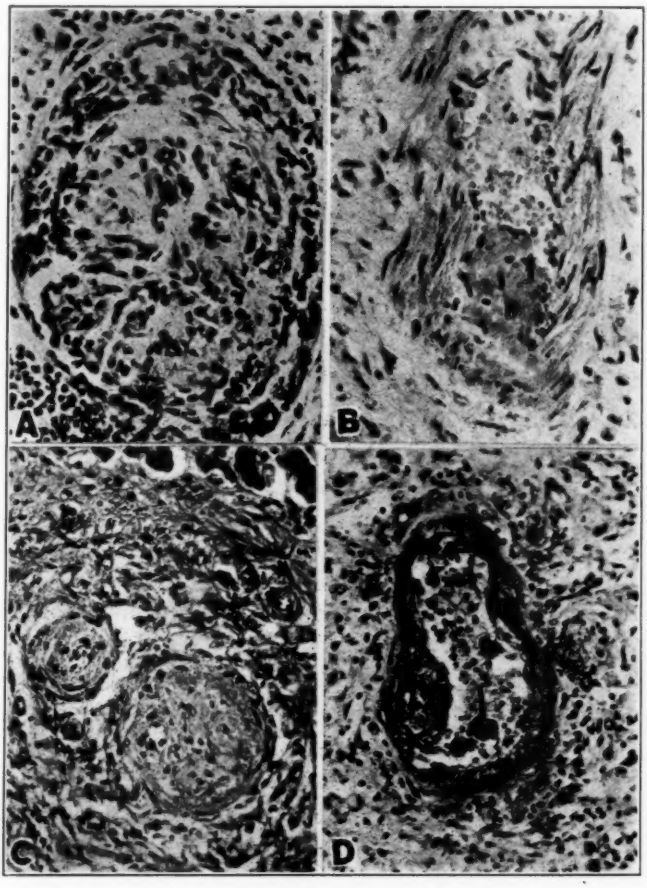


Fig. 2 A, B, C, D

A. Subacute diffuse glomerulonephritis in a bacteria-free case of subacute bacterial endocarditis. Blood cultures were negative and no bacterial colonies were to be found in the vegetations. All glomeruli were in the same stage of the process. Death was due to renal insufficiency.

B. Arterial lesion in the myocardium in patient dying of acute diffuse glomerulonephritis. Necrosis of a portion of the wall, occlusion of part of the lumen with platelet thrombus undergoing organization.

C. Arterial lesions in the liver in acute diffuse glomerulonephritis. Necrosis of the wall of some arterioles and small arteries with complete occlusion of the lumen.

D. Complete necrosis of the wall of a blood vessel in the adrenal in a case of acute diffuse glomerulonephritis.

wave inversions indicative of serious myocardial damage (Master[8]) (Fig. 2 B). If the myocardial damage is severe, intense dyspnea and cyanosis may dominate the clinical picture of the first few weeks. The venous pressure rises and there are physical signs of acute passive congestion in the lungs and liver. At times congestive heart failure may end in death within the first week or two after the onset, before the renal damage has resulted in a significant degree of azotemia.

Cardiac disturbances of this severity are due to vascular injuries affecting capillaries and arterioles of the myocardium. There is often interstitial edema, but morphological changes in the endothelium of the interstitial capillaries may be difficult to demonstrate. If the cardiac damage has been sufficiently severe, lesions of small branches of the coronary arteries can be found microscopically (Fig. 2 B). These lesions may consist of necrosis of arterial walls, infiltrations of the media and adventitia with inflammatory cells, proliferative and desquamative lesions of the intima and obliteration of the lumen by thrombi (Fig. 2 B). The vessel lesions are probably the result of acute damage and occlusion of capillaries and vasa-vasorum in the walls of the affected arteries.

Similar arterial lesions may be found in the liver, the brain or in any of the viscera (Fig. 2 C and D). Cerebral disturbances which sometimes characterize the first weeks of the disease may be due, at least in part, to such vascular injury. Patients who recover from a severe attack of acute glomerulonephritis may suffer in after years from the late results of the extrarenal vascular lesions.

The Significance of the Renal Damage.—In many patients who succumb to acute glomerulonephritis it is often difficult to demonstrate morphologic changes in the walls of capillaries of other organs than the kidney although clinical evidences of disturbances in capillary function previously existed. In the kidney, the peculiar arrangement of the capillaries of the glomeruli predisposes this organ to more profound and permanent damage. Swelling of the endothelium of the glomerular capillaries is much more important anatomically and functionally than is swelling of capillary endothelium in other organs and tissues of the body. The Bowman's capsule which envelops each glomerulus can stretch very little. For this reason swelling and proliferation of glomerular endothelial cells results in complete obliteration of the capillary lumen, so that the glomeruli become bloodless. Glomerular function and therefore renal function is promptly disturbed, for the glomeruli are the essential excre-

tory units. The bloodless condition of glomerular tufts soon results in necrosis of portions of various glomeruli and this destruction is apt to be permanent.

Since Reichel[9] and Loehlein[10], pathologists, have emphasized the significant fact that every glomerulus is more or less involved, some severely or perhaps totally destroyed, others less severely affected so that some measure of anatomical and physiological recovery is possible. The term acute diffuse glomerulonephritis was chosen in order that the generalized nature of the process should not be forgotten.

Almost the entire circulation of the kidney must pass through the glomeruli before it enters a secondary system of capillaries which nourishes the delicate tubules (Peter[11]). The inability of much of the blood to pass the obstructions in the glomeruli results in damage to the tubules. Although the tubules have a great capacity to regenerate (Thorel[12]), they cannot do this very successfully as long as they receive an inadequate blood supply. Therefore cellular destruction of the regenerating tubules continues for some time, even for many months, while the circulation through the glomerular tufts slowly becomes re-established.

This results in the daily loss of great quantities of albumin, casts and cellular detritus. Patients who have survived the acute attack may subsequently develop marked hypoproteinemia and general anasarca due to the prolonged loss of albumin (Epstein[13]).

Twenty-five years ago there was much discussion concerning a rarer disease of the kidney, a pure tubular damage, for which Friedrich Müller[14] had advocated the term nephrosis. In this condition, prolonged loss of albumin in the urine also results in hypoproteinemia and anasarca. The clinical picture is therefore identical with that of the subacute stage of Bright's disease except that there is no history of an acute onset following scarlet fever or other streptococcus infection, no hypertension or history of hypertension at the onset and no red blood cells in the urine. Unfortunately, any or all of these characteristic symptoms may be absent in the waterlogged stage of subacute glomerulonephritis and the differential diagnosis from nephrosis is then difficult.

Popular interest in this rare disease was responsible twenty years ago for the fact that it became confused in the minds of physicians with that common clinical syndrome which had been described so well by Bright in 1827. Under the influence of Volhard[15] the well known clinical picture of the waterlogged patient with subacute Bright's disease has been re-

named, quite unnecessarily, the nephrotic stage of glomerulonephritis. The term is merely a synonym for Delafield's chronic parenchymatous nephritis, which is the parenchymatous stage of chronic glomerulonephritis.

The Final Hypertensive Stage.—Patients who have had glomerulonephritis have suffered a severe and permanent damage to the kidney. Even though recovery may seem to have been complete so that for years no albumin or only a trace persists in the urine, the kidney remains susceptible to toxic damage. Pregnancy or an intercurrent infectious disease may precipitate a recurrence of marked albuminuria, edema and hypertension. Often arterial hypertension develops insidiously. Later there may appear a tendency to fixation of specific gravity or a reduction in urea clearance as evidence of progressive contraction of the kidneys. Ultimately, the nitrogenous constituents of the blood may begin to mount until the patient finally succumbs to the increasing azotemia.

The terminal picture of chronic Bright's disease is clinically indistinguishable from the terminal picture of primary hypertensive renal disease. In both, a long standing hypertension terminates in azotemia (dry uremia) due to progressive renal insufficiency. This clinical similarity in the termination of two diseases, so dissimilar in primary etiology and in their early stages, has been, and still is, a source of much confusion. The explanation is to be found in a study of the progressive changes in the arterial supply of the kidneys in both conditions and its influence in slowly reducing the remaining renal parenchyma (Baehr and Ritter[16]).

In both diseases progressive vascular changes are characteristic of the later stage (Fig. 3). Numerous arterioles become thickened and sclerosed and the lumen of many of them becomes progressively narrower until completely occluded. The resulting ischemia affects many small areas of renal parenchyma so that they gradually become atrophic and sclerosed. Between these many sclerotic contracting areas, alternate areas of still functioning renal tissue carry on urinary excretion until the disease has finally progressed so far that insufficient functioning tissue remains.

In primary hypertensive renal disease, the fine vascular occlusions are scattered uniformly throughout the kidney, so that it gradually becomes contracted into a finely granular organ. In this primary contracted kidney of essential hypertension, the vascular disease develops in a previously normal organ. In the secondary contracted kidney of chronic Bright's

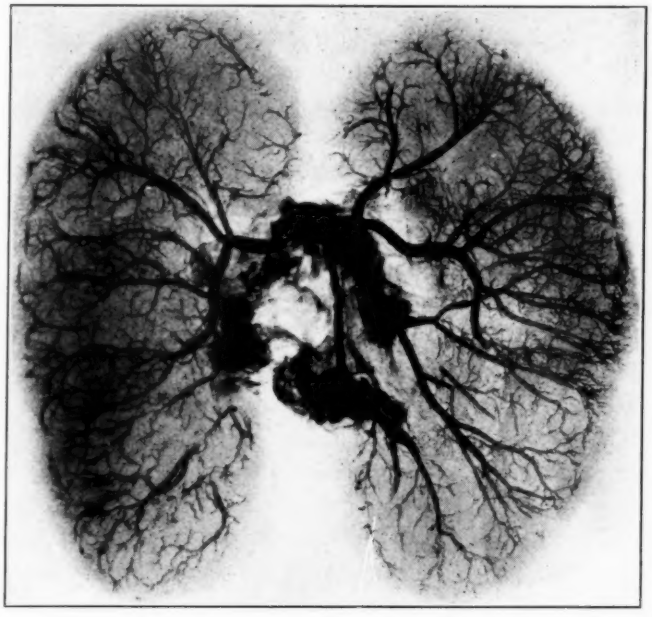


Fig. 3—The kidney in chronic diffuse glomerulonephritis. Arterial tree injected with a barium gelatin mixture and then x-rayed. Note the marked reduction in vascularity due to progressive closure of arterioles and small arteries throughout the organ. The resulting progressive ischemic sclerosis of the renal parenchyma in chronic diffuse glomerulonephritis is identical in its effect with that of primary vascular disease of the kidney, the arteriolar nephrosclerosis of essential hypertension.

disease, the areas of functioning parenchyma between the numerous islands of ischemic sclerosis are already diseased and therefore function imperfectly. Renal insufficiency and death in uremia will therefore occur in chronic Bright's disease long before a degree of renal contraction has been reached which is comparable to that of the primary contracted kidney. For this reason, the secondary contracted kidney at autopsy is a somewhat larger organ than the primary contracted kidney. In both, however, the cause of the contraction is identical, the slowly progressive reduction in functioning renal parenchyma due to the vascular disease. There are some cases of chronic glomerulonephritis in which the atrophy is the result chiefly of the inflammation and secondary

cicatrization without significant vascular alterations.

Pathogenesis.—Glomerular lesions resembling human glomerulonephritis were produced experimentally in 1913 by Baehr[17] and by Christian and O'Hare[18] by the intravenous injection of uranium nitrate. These lesions were the direct result of the injected toxin upon the endothelium of the glomerular capillaries. The experiments threw no light upon the mechanism of Bright's disease for the following reasons.

Acute diffuse glomerulonephritis is almost invariably a sequel of some streptococcus infection such as scarlet fever, but it does not occur during the active period of the disease when the organisms or their bacterial toxins are reaching the kidneys in greatest concentration. Escherich and Schick [19] emphasized in 1912 that glomerulonephritis most commonly occurs during the second week after recovery. This important observation has received renewed emphasis during recent years as a result of the work of Lyttle[20]. By means of Addis counts on the urine of scarlet fever patients, he demonstrated that most of them show a sudden explosive outpouring of albumin, casts or red blood cells some time during the second week of convalescence, most commonly between the nineteenth and twenty-second day after the onset of the disease.

To explain this time relationship, Escherich and Schick, and later Friedemann and Deicher[21], advanced the hypothesis that glomerulonephritis is an allergic reaction to the infecting organism. Recently, Longcope[22] demonstrated the presence of a high titer of streptolysins in the blood of patients suffering from postscarlatinal nephritis. However, a high titer of streptolysins is also frequently found in patients with rheumatic fever, a disease which is no longer thought to be due to allergy to the streptococcus. The hypothesis that glomerulonephritis is a local tissue reaction to a stage of bacterial allergy is still theoretical and as yet devoid of conclusive experimental support.

The nearest approach to experimental evidence is the recent work of Lukens and Longcope[23]. They have been able to reproduce glomerular lesions which resembled glomerulonephritis by the intra-arterial injection of streptococcus vaccine into rabbits which had previously been "sensitized" by intradermal injections of living streptococci. The presence of skin reaction to filtrates of hemolytic streptococci provided some evidence in Longcope's interesting experiments that the previous intradermal injections of living streptococci had actually "sensitized" his rabbits in the allergic sense. However, the pathological process involved

in glomerulonephritis is not a recognized characteristic of the known states of bacterial allergy.

The work of Masugi[24] supplies still another possibility for speculation concerning the pathogenesis of glomerulonephritis. By means of the intravenous injection of heteronephrotoxic serum into laboratory animals, Masugi and more recently Smadel and Farr[25] have experimentally reproduced glomerulonephritis and even the chronic stages of Bright's disease. An hypothesis might therefore be proposed that products of cellular destruction caused by damage to the renal parenchyma during scarlet fever might act antigenically during convalescence and give rise to specific nephrotoxic substances. Such a theory is hardly plausible for destruction of renal parenchyma by diseases other than streptococcal infections does not give rise to glomerulonephritis. Moreover, streptococcal infections themselves, no matter how prolonged, do not cause glomerulonephritis unless the streptococci are killed off *and* the patient recovers from the infection.

This is best illustrated by our observations on streptococcemia and streptococcus endocarditis[26]. Among fifty-three consecutive patients with Streptococcus hemolyticus bacteriemia which came to autopsy, no instance of acute diffuse glomerulonephritis was found. Among ninety patients with subacute bacterial endocarditis in which the Streptococcus viridans was constantly demonstrable in the blood for months throughout the course of the disease, only one instance of acute glomerulonephritis was found postmortem.

In striking contrast to the negative findings in 143 cases of persistent streptococcemia is our experience with patients who recovered from a streptococcus infection. Among fifty-seven patients with subacute bacterial endocarditis who had killed off their bacteria and who died subsequently in the bacteria-free stage of the disease, diffuse glomerulonephritis occurred and was responsible for a uremic death in nineteen patients, an incidence of 33.3 per cent (Fig. 2 A). One died of acute glomerulonephritis; the other eighteen succumbed in the subacute or chronic stage of typical glomerulonephritis.

From these experiences, we can conclude that acute Bright's disease cannot be due to the direct damaging effect of streptococci or their toxins upon the kidney. Nor can it be caused by the mere killing off of streptococci, for this must be taking place constantly in patients with prolonged streptococcemias. It is evident that the sudden explosive occur-

rence of acute diffuse glomerulonephritis is a specific reaction, concerned in some still unknown manner with the mechanism of recovery from streptococcal infections.

BIBLIOGRAPHY

1. Bell, E. T. *Am. J. Path.*, 1936, *12:* 801-824; 1937, *15:* 497-552.
2. Baehr, G. and Schifrin, A. *Libmann Anniv. Vols.*, 1932, *1:* 125-131.
3. Baehr, G. *Tr. A. Am. Physicians*, 1931, *46:* 87-95.
4. Loehlein, M. *Med. Klin.* (Berlin), 1910, *6:* 375-379.
5. Baehr, G. *J. Exper. Med.*, 1912, *15:* 330-346.
6. Baehr, G. *Arch. Int. Med.*, 1921, *27:* 262-264.
7. Baehr, G. *J.A.M.A.*, 1926, *86:* 1001-1004.
8. Master, A. M., Jaffee, H. L. and Dack, S. *J. Mt. Sinai Hosp.*, 1937, *4:* 98-102; and *Arch. Int. Med.*, 1937, *60:* 1016-1027.
9. Reichel, H. *Zeitschr. f. Heilkunde*, 1905 *6:* 72-103.
10. Loehlein, M. *Arb. a.d. pathol. Inst. z. Leipzig*, 1907, v. *4*, 98 pp.
11. Peter, K. *Untersuchungen über Bau und Entwickelung der Niere.* Jena, Fischer, 1909, v. *1.*
12. Thorel, C. *Deutsch. Arch. f. klin. Med.*, 1903, *77:* 29-68; 1905, *84:* 173-188.
13. Epstein, A. A. *J. Exper. Med.*, 1914, *20:* 334-345; and *J.A.M.A.*, 1917, *69:* 444-447.
14. Müller, F. *Verhandl. deutsch. path. Gesellsch.*, 1905, *6:* 64-99.
15. Volhard, F. and Fahr, T. *Die Brightsche Nierenkrankheit*, Berlin, Springer, 1914.
16. Baehr, G. and Ritter, S. A. *Arch. Path.*, 1929, *7:* 458-472.
17. Baehr, G. *Beitr. z. path. Anat.*, 1913, *55:* 545-574.
18. Christian, H. A. and O'Hare, J. P., *J. Med. Research*, 1913, *28:* 227-234.
19. Escherich, T. and Schick, B. *Scharlach.* Vienna, A. Hölder, 1912.
20. Lyttle, J. D. *J. Clin. Investigation*, 1933, *12:* 95-103.
21. Friedemann, U. and Deicher, H. *Ztschr. f. klin. Med.*, 1928, *108:* 737-746.
22. Longcope, W. T. *Bull. Johns Hopkins Hosp.*, 1929, *45:* 335-360.
23. Lukens, F. D. W. and Longcope, W. T. *J. Exper. Med.*, 1931, *53:* 511-526.
24. Masugi, M. *Beitr. z. path. Anat. u. z. allg. Path.*, 1933, *91:* 82-112; and Masugi, M. and Sato, Y. *Virchows Arch. f. path. Anat.*, 1934, *293:* 615-664.
25. Smadel, W. and Farr, L. E. *J. Exper. Med.*, 1937, *65:* 537; 541.
26. Baehr, G. *Tr. A. Am. Physicians*, 1931, *46:* 87-95.

CLINICAL ASPECTS OF NEPHRITIS*

ROBERT F. LOEB

Professor of Medicine, College of Physicians and Surgeons

THE TERM nephritis embraces a number of morbid states with widely diversified etiological, pathological and clinical characteristics. An attempt to discuss the clinical aspects of various types of Bright's disease this evening would be futile. Likewise, a discussion of the symptomatology of one or more forms of nephritis could serve no constructive purpose. Consequently, I have elected to limit myself to the consideration of certain problems concerning that entity commonly known as glomerulonephritis.

All recent studies indicate that there is, as a rule, a close relationship between infection of the upper respiratory tract and the onset of acute glomerulonephritis. In recent and carefully controlled studies in which bacteriological and immunological observations have been made, the onset of acute glomerulonephritis has, in the vast majority of instances, been found to be associated with evidence of infection by the hemolytic streptococcus (Group A of Lancefield). Thus, Seegal and his coworkers found that the antistreptolysin titer of the blood was significantly increased in seventy-six of eighty consecutive patients suffering from acute glomerulonephritis, and in most of the cases it reached amazingly high levels. Longcope reported the presence of infection with the hemolytic streptococcus in 95 per cent of his patients.

In other instances, it now seems certain that acute glomerulonephritis develops secondary to infections due to agents other than the hemolytic streptococcus. A number of cases of acute nephritis have been reported following pneumococcal pneumonia. In most of these, secondary streptococcal infection has not been eliminated as a possible cause, but Seegal has recently followed two cases of postpneumonic nephritis in which there was no evidence of secondary streptoccal infection as determined by repeated antistreptolysin measurements. In bacterial endocarditis due

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital. Delivered November 3, 1937 in the Tenth Annual Graduate Fortnight

to the streptoccus viridans also, glomerulonephritis not infrequently develops and is superimposed upon embolic nephritis without bacteriological or immunological evidence of invasion by the hemolytic streptococcus. It seems probable that in rare instances, acute glomerulonephritis may be initiated by still other organisms and that these need not necessarily gain entry to the body through the respiratory tract.

The role of infection in the etiology of *chronic* glomerulonephritis is far less clear than in the acute form of the disease, although exacerbations of chronic nephritis accompany or follow intercurrent infection with the streptococcus hemolyticus with striking regularity. In contrast with acute glomerulonephritis which usually develops ten to twenty days following an acute infection, chronic nephritis usually develops so insidiously that its onset is, as a rule, unrecognized. It seems certain that many cases of chronic nephritis begin as acute glomerular nephritis but the actual per cent is difficult to determine as it is often impossible to differentiate between the onset of acute nephritis and the exacerbation of an apparently quiescent chronic process. In Longcope's series about 40 per cent of the patients with acute nephritis developed active and progressive chronic nephritis. On the other hand, Lyttle, in studying children, in whom the outlook is admittedly favorable, has found that less than 5 per cent develop the chronic form of the disease.

In addition to the fact that chronic nephritis usually develops without definite relation to a preceding acute infection, there are also immunological differences between this and the acute form of the disease. Whereas the antistreptolysin titer of the blood may increase in chronic nephritis associated with streptococcal infection, it rarely reaches the high levels seen in acute nephritis. The significance of this difference in the immune response in the acute and chronic forms of the disease remains to be determined.

Mechanism of Glomerulonephritis.—While the relationship of hemolytic streptococcal infection to the onset of nephritis, at least in the acute form, is recognized, this knowledge has not as yet materially advanced our understanding of the mechanisms involved in the genesis of the disease. The fact that the onset of acute nephritis does not accompany but rather follows an acute infection offers evidence against the idea that the disease results from direct and immediate damage of the kidneys by bacteria or bacterial products. In 1912, Escherich and Schick expounded the idea that acute nephritis was not caused by acute infection but by

the immune reactions resulting from it. This concept may offer a satisfactory explanation for the latent period which elapses between the onset of infection and the onset of nephritis.

There have been many futile attempts to produce a disease in animals which shares the characteristics of glomerulonephritis in man. However, one line of approach, begun in 1900 by Lindemann and by Pierce in 1904 and elaborated by Masugi in 1929 and by Smadel and Farr since that time, has yielded interesting and important results. The general technique employed by these investigators is based upon the principle of the development of organ-specific antisera. If an emulsion of normal rat kidney is repeatedly injected into the peritoneum of a rabbit, a rabbit anti-rat kidney serum is produced. If one, two or three doses of this serum are injected intravenously into rats, acute nephritis develops. This disease may heal completely or it may go on to a chronic form associated with persistent and progressive albuminuria, cylindruria, edema, hypertension, anemia, nitrogen retention and a fatal decrease in renal function. The renal lesions bear a close resemblance to chronic glomerulonephritis in man.

The most significant feature of these studies is that they demonstrate the possibility of initiating chronic and progressive renal disease through the action of a single insult, in this case a dose of antikidney serum injected into a normal animal. Of added interest is the recent and important observation of Farr and Smadel that the course of the nephritis induced by the injection of nephrotoxic serum can be influenced by the amount of protein in the diet. If the diet of the rats contains only 5 per cent protein, the acute nephritis heals with great regularity in about three weeks. If, on the other hand, the diet contains 40 per cent protein, the disease progresses and the animals all die of chronic nephritis.

It is tempting to infer that a mechanism similar to that described in rats is responsible for glomerulonephritis in man. In order to extend the analogy, we must hypothecate that the hemolytic streptococcus or other bacteria produce somewhere in susceptible human beings nephrotoxic sera. These may give rise to acute nephritis which may or may not become chronic. It is possible that in man, as in the rat, another factor such as that of protein ingestion may serve to make progressive the disease initiated by a nephrotoxic serum. There is unfortunately, at the present time, no experimental evidence suggesting that nephrotoxic sera can be developed in response to the injection of bacterial products.

This speculative discussion has no practical application, but it indicates the trend of present day thought in relation to the possible mechanism involved in the production of glomerulonephritis. However, the observations on the deleterious effect of large amounts of protein in the diet are sufficiently striking to reopen the question of the place of protein in the diet in human nephritis.

The *diagnosis* of acute glomerulonephritis in its characteristic form offers but little difficulty. When, however, albumin, casts and red blood cells appear in the urine in small but definite quantities without extrarenal signs, either during or after an acute infection, the problem of diagnosis becomes difficult or even impossible. A number of students of nephritis circumvent these diagnostic dilemmas by applying the term focal nephritis to these doubtful cases, but in the writer's opinion the introduction of another term does not clarify the issue. If mild albuminuria, cylindruria and microscopic hematuria persist for more than one or two weeks, it seems probable that acute glomerulonephritis is present. If the changes disappear in a shorter time, it is best to admit that the diagnosis is uncertain. Minute decreases in renal function as measured by the urea clearance test may result from disorders other than nephritis and do not alone simplify the diagnostic problem. Frequently, often repeated urine examinations, a careful record of body weight which, in the absence of visible edema, may give evidence of water retention or diuresis and numerous blood pressure determinations may give transient but convincing evidence favoring the diagnosis of acute glomerulonephritis.

The difficulties besetting the physician in establishing a diagnosis of acute glomerulonephritis are emphasized by recent studies of urinary changes in acute rheumatic fever and in scarlet fever. In the former, in at least 15 per cent of the patients with the active form of the disease, red blood cells and small amounts of albumin appear in the urine at some time and yet only about 3 per cent prove to have associated acute glomerulonephritis at death. In scarlet fever, Lyttle, applying Addis' quantitative method for the determination of protein, casts and cells in the urine, found consistently a moderate transient increase above the accepted limits of normal. This occurred between eight and forty-five days after the onset of the attack of scarlet fever. Lyttle found similar changes in the urine after other infections due to the streptococcus hemolyticus, but did not find them with any regularity after infection with

other organisms. It seems unlikely that all patients suffering from scarlet fever and other streptococcal infections develop acute glomerulonephritis. Whether or not, however, the difference between this micronephritis or "renal irritation" and true acute glomerulonephritis is qualitative or quantitative cannot be settled at this time.

The *differentiation between acute glomerulonephritis and the chronic form of the disease* is of great importance because of the difference in prognosis and therapeutic indications. If urine examinations happen to have been made just prior to the onset of the attack, the problem is of course simple. Without knowledge of the medical background of the patient, it is often difficult and occasionally impossible to tell whether the patient's disease represents the beginning of acute nephritis or an acute exacerbation of chronic glomerulonephritis. If the latent period between acute infection and the appearance of renal disease is greater than ten days, it favors the diagnosis of acute nephritis because, in the chronic form of the disease, the flare-up usually occurs during the acute infection or shortly thereafter. When the signs of advanced and protracted renal disease are present, the diagnosis of chronic nephritis is justifiable. In the absence of these guides, diagnosis frequently has to be deferred until the subsequent course has been observed.

Patients with acute glomerulonephritis either recover completely or their disease progresses to the chronic form or they die during the acute attack. A fatal outcome occurs in less than 5 per cent of the cases. In children, complete recovery occurs in about 90 per cent of hospitalized patients but in adults the prognosis is definitely less favorable. However, it is difficult to determine the actual incidence of recovery because, as has been stated, an apparent acute nephritis may in reality represent an exacerbation of the chronic form of the disease, hitherto unrecognized. Furthermore, many patients with mild acute nephritis undoubtedly recover without ever coming to the attention of a physician and are consequently not included in statistical studies. Finally, in a number of mild cases, it is impossible to be certain that nephritis is present. Be that as it may, estimates of the frequency of recovery in adults vary from about 15 to 70 per cent.

It is impossible to predict the outcome of acute glomerulonephritis early in its course. However, in those instances in which the constitutional symptoms of the preceding infection have been severe, it appears to be particularly good. Furthermore, complete recovery occurs rapidly

in many patients even though they present alarming extrarenal manifestations early in the course of the disease, whereas chronic nephritis develops in others with an apparently benign form of the disease. When significant impairment of renal function persists for more than 3 or 4 months, the outlook for complete recovery is almost invariably bad.

The duration of the attack of acute glomerulonephritis varies enormously. In a number of cases, even when the diagnosis appears established beyond doubt, complete recovery may occur in the course of a few days. In other cases the disease may persist for more than a year and still terminate favorably. In these cases the extrarenal manifestations of edema, hypertension and nitrogen retention disappear, as a rule, in the course of a few weeks and the persistence of the disease process is demonstrable by the urinary changes alone.

According to Longcope and others, the duration of an attack of acute nephritis and the tendency to chronicity are definitely related to the persistence of infection by the hemolytic streptococcus. However, Seegal and his coworkers find that in a number of patients, the disease progresses in the absence of persistent or recurrent bacteriological or immunological evidence of infection. Furthermore, they have found that recovery may occur despite the persistence of definite infection.

Of great academic interest and also of great importance for the peace of mind of the patient is the fact that once completely recovered, i.e., after the disappearance of albumin, red cells and casts from the urine, there appears to be no danger of the development of chronic nephritis. Thus, E. N. Loeb, Seegal, Lyttle and Jost have shown in a series of eight patients, that following recovery from acute glomerulonephritis a second infection caused no return of nephritis. In these patients, the infection preceding the onset of the attack of acute nephritis and the second infection occurring after complete recovery were proven bacteriologically and by means of antistreptolysin determinations to be due to the streptococcus hemolyticus. In three other patients, transient hematuria or albuminuria or both developed with the second infection, but none of the eleven patients developed chronic glomerulonephritis.

I should like now to discuss a few points in relation to the diagnosis of chronic glomerulonephritis. The diagnosis is, as a rule, easily established on the basis of the continued presence of albuminuria, cylindruria and varying degrees of hematuria either with or without the extrarenal manifestations of the disease. At times, however, it presents a trying

problem and the difficulties in distinguishing the acute and chronic forms of the disease have been mentioned. The differentiation between chronic glomerulonephritis and arteriolar nephrosclerosis is sometimes impossible but is of little importance except for academic reasons.

The differentiation between the nephrotic phase of chronic glomerulonephritis and true nephrosis also offers difficulties and is of importance because in the latter complete recovery takes place in about 50 per cent of the cases. Both conditions have in common, massive albuminuria, edema, decrease in the serum protein content with a tendency toward inversion of the albumin-globulin ratio, lipemia and often lowering of the basal metabolic rate. The diagnosis of chronic nephritis becomes probable if, in addition to these signs, there be enlargement of the heart, marked hypertension, changes in the eyegrounds, significant impairment of renal function or numerous red blood cells in the urinary sediment. The age of the patient also has significance since true nephrosis rarely occurs in adults. The difficulties encountered in the diagnosis are exemplified by the following case record. A boy of fourteen developed headaches and edema about two weeks after a head cold. On examination, he had massive edema, and a blood pressure level which reached 160/100. His urine showed the presence of large amounts of albumin, many casts and occasional red cells. His blood urea rose to 100 mg. per 100 cc. This patient was believed to have chronic glomerulonephritis of the nephrotic type. He subsequently died from pneumococcus peritonitis and examination postmortem demonstrated the presence of pure lipoid or true nephrosis.

The differentiation between latent glomerulonephritis and orthostatic albuminuria presents difficulties in adolescents in whom no significant disturbance of renal function can be determined by the usual tests. The evidence favors an orthostatic process if the albuminuria disappears with bed rest but this is, however, not entirely conclusive, as the albuminuria in some cases of latent nephritis may diminish greatly with rest and increase with activity. If hypertension or other extrarenal manifestations are present, the problem of diagnosis is simple. In a number of cases, only prolonged observation with repeated urine examinations will serve to clarify the diagnosis.

It must be borne in mind that the picture of advanced renal insufficiency often results from kidney disease other than chronic nephritis. In those cases in which the history is in doubt, and in which pyuria plays

a prominent part, if bouts of fever have been present or if the clinical picture is in any way unusual, it is essential that x-ray examination and pyelography be employed.

Finally, it should be recognized that albuminuria, casts and red blood cells appear in the urine in cardiac decompensation, in jaundice and in severe febrile disease. Thus, in cardiac insufficiency, in addition to the urinary changes described, the blood urea may reach 0.70 gm. per l. or more, the blood urea clearance may be diminished and the phthalein excretion often falls to 30 per cent or even less. Hence, it is often impossible to state whether chronic nephritis is or is not present and decision must be postponed in such patients until cardiac compensation is re-established. If eyeground changes, fixation of the specific gravity of the urine, and marked hypertension accompany cardiac failure, it is probable that nephritis is also present.

While the *prognosis* in patients with chronic glomerulonephritis is ultimately bad, the velocity with which the disease reaches its fatal termination is extremely variable. Except in the terminal stages, it is practically impossible to predict the probable life span of a patient on the basis of clinical observations and laboratory studies, made at any one time. Repeated observations and studies of renal function made over a period of months or years are of far greater value insofar as they may reveal an approximate curve of the velocity of progression of the disease. Despite the most careful supervision, however, prediction of the course of chronic glomerulonephritis is hazardous. For example, a patient may be observed during an acute exacerbation of the disease. After some months, activity may subside and the patient may lead a normal and useful existence for many years before uremia develops. Thus, in a patient seen at the Presbyterian Hospital with massive edema, hypertension, nitrogen retention, albuminuria and hematuria, the blood pressure now, twenty years later, is normal and only albuminuria and cylindruria without impairment of renal function persist. In other cases of apparently the same initial severity, the disease may progress to a fatal termination in a few months.

There are certain criteria, which although not infallible, have real prognostic value. When the disease is associated with rapidly progressing hypertension, when severe anemia develops abruptly, when in the course of a few months the power of concentration is lost and when activity of the disease as manifested by copious microscopic hematuria persists

over a period of three to four months, the duration of life is usually less than two years. Furthermore, if decompensated renal function appears and the blood urea rises progressively to levels of perhaps 1 gram per l. the prognosis is equally grave. The presence of papilledema, combined with hemorrhages and patches of exudate in the eyegrounds also usually indicates that the duration of life will be less than two years. The same outlook may be anticipated when the urea clearance falls below 10 per cent of normal or when the phthalein excretion fails completely.

In order to temper the significance of these dogmatic statements, I should like to mention briefly the record of one patient who broke all the accepted rules. In this girl, after six years of active glomerulonephritis, the excretion of phthalein in two hours was nil, her blood urea was 90 mg. per 100 cc. and her creatinine was 6 mg. per 100 cc. Despite this, the patient worked most of the time during the following six years and annual observations showed not only the persistence of markedly impaired renal function but further accumulation of urea in the blood. The patient finally died in uremia and the diagnosis was confirmed at autopsy. Cases of this kind occur with sufficient frequency to warrant extreme caution in offering a bad prognosis for the probable duration of life.

Before concluding, I should like to comment briefly on the *treatment* of chronic nephritis. It must be recognized that, in the treatment of chronic glomerulonephritis, we are dealing with the problem of therapy in a disease which is incurable at the present time. Hence, the physical comfort of the patient and, still more important, his peace of mind, deserve first consideration. If this principle be kept in mind, the patient may be spared the distress and discomfort associated with measures such as unnecessary dietary restriction, excessive purging, sweating and colonic therapy which are not only futile but which may be actually harmful. This apparent therapeutic nihilism, I believe, in reality better serves to make the patient's existence tolerable than does over-energetic treatment. This point of view does not imply that a purely laissez faire attitude should be adopted. On the contrary, every effort should be made to introduce those measures which may retard the progress of the disease and it is essential that the patient be forewarned against those factors which appear to accelerate it.

In the *dietetic treatment* of chronic nephritis only questions of protein, salt and fluid deserve consideration. It is our impression that the

importance of *protein* restriction in some cases and of forced protein feeding in others has been over-emphasized in recent years. In chronic nephritis, characterized by albuminuria, cylindruria and some hematuria without edema or advanced renal insufficiency, there appears to be no reason for regulating the amount of protein in the diet beyond suggesting that the patient follow the adage of "moderation in all things." In the presence of nitrogen retention, the amount of protein should be restricted because large amounts undoubtedly contribute to the retention of nitrogenous products. In these patients, the amount of protein may perhaps ideally be reduced to 40 or 50 grams a day. If, however, anorexia results in loss of weight and strength, it is far better to allow the patient to choose his foodstuffs without regard to theoretical consideration than to have him burn his own body protein and increase his non-protein nitrogen retention from that source.

When Epstein pointed out the importance of hypoproteinemia in the genesis of nephrotic edema twenty years ago, he logically introduced high protein feeding to compensate for protein lost in the urine. We all employ this diet today in the treatment of the edematous chronic nephritic, but I think it is fair to say that we are almost always disappointed in its effect upon the level of the serum proteins and amount of edema present. Nevertheless, it seems rational to attempt to maintain nitrogen balance in these patients in order to prevent the further depletion of serum albumin. This can usually be accomplished by the ingestion of about 100 to 120 grams of protein a day. I sincerely doubt that diets much higher in their protein content accomplish more and, in addition, they are distasteful to the patient deprived of salt.

Our feeling concerning the place of salt restriction can be expressed in a few words. Sodium salts are essential for the formation of edema fluid. Hence, in the presence of abnormal fluid retention, regardless of the reason for its appearance, rigid limitation of sodium must be enforced. It is our opinion that there is no other sound basis for salt restriction in the treatment of nephritis and that employment of this therapeutic measure in the absence of edema often accentuates anorexia, nausea and vomiting.

In patients with chronic nephritis, consideration of *fluid* ingestion is important only under two conditions. First, in the presence of edema, the intake of water should be restricted in accordance with the degree of retention, the acuteness of the symptoms and the presence of cardiac

insufficiency. Second, with the advance of renal insufficiency, the fluid intake should be increased to compensate for the loss of the power of concentration. If, however, the intake of fluid exceeds that amount which can be eliminated by the renal units still capable of function, edema will appear.

The use of diuretics is contraindicated in patients with chronic nephritis exhibiting either hematuria, gross or microscopic, or significant impairment of renal function.

The importance of the close relationship between recurrent or persistent infection of the upper respiratory tract and exacerbations of chronic nephritis can not be over-emphasized. Both the physician and the patient must look upon even a mild cold as a matter of concern and should treat the disorder accordingly. Tonsillectomy, in my opinion, should be performed routinely in patients with early nephritis and sinusitis merits rigorous attack. When, however, glomerulonephritis has progressed to the stage of advanced renal insufficiency, operative treatment of disease of the nose and throat has no place.

In conclusion, I should like to say that this brief sketch of certain aspects of glomerulonephritis in no way does justice to the scope of the title and I must add that I have considered only a few phases of the disease which seem to have particular interest at the present time.

CALCULOUS DISEASE IN THE URINARY TRACT*

The Formation of Stone

LINWOOD D. KEYSER

Surgeon, Roanoke General Hospital, Roanoke, Virginia

THE PROCESS of stone formation in the urinary tract has been one of the most elusive of medical problems. Prior to 1917, when Osborne, Mendel and Ferry made the chance observation that rats fed on a diet deficient in vitamin A developed urinary calculi, little purposive effort at solving the problem had been made. Through the ages, it is true, that man speculated with vagaries of the imagination concerning water, the soil, uric acid and lime excretion as etiologic factors. Latterly with the development of the modern concept of bacterial infection, of urostasis, and of metabolic disorder, hypothetic consideration of the influence of these agencies has been championed by many clinicians. Since 1920 a series of experimenters and clinicians have diligently approached the problem in the laboratory and at the bedside. While the chemists and bacteriologists have been of help, it is interesting to note that many of our best contributions have come from the urologist himself who has at least investigated, stimulated, and actively helped his colleagues in the basic sciences.

What do we know of lithiasis today? It shall be my purpose to correlate the pertinent data which has aggregated in the last few years and to establish the thesis that stone may arise in several ways: that it is an end result of several types of colloidal crystalline aggregation into a solid mass. I shall attempt to show the grosser features of some of these processes and finally to point out how far we may attempt to control stone disease within the limits of our present scientific knowledge.

THE COLLOID–CRYSTALLOID PRECIPITATION MECHANISM
CRYSTALLINE HYPEREXCRETION AS A CAUSE OF STONE

Stone arises when colloids and crystalline matter are simultaneously precipitated in the free urinary stream. The colloidal gel enmeshes

* Delivered November 9, 1937, in the Tenth Annual Graduate Fortnight

agglutinated or fusing crystals and forms the organic framework around and within which these crystals are laid down as building elements. The process may be stimulated, first by the hyperexcretion of excessive crystalline material through the kidneys beyond the power of the urine with a given pH, colloid and salt content to maintain solubility; second, by the entrance of foreign colloid into the urinary stream. Hypothetically we must consider further the possibility of stone formation by the precipitation of normal colloid from the state of a sol to that of a gel by factors which are as yet unknown.

The scientific establishment of the colloid crystalloid precipitation mechanism rests on the following facts:

1. Crystalloids, e.g. calcium oxalate, precipitated from colloidal solutions in vitro change from isolated noncoalescent crystals to those of fusing stone forming type. (Rainey, Ord, Shattock). (Fig. 1).

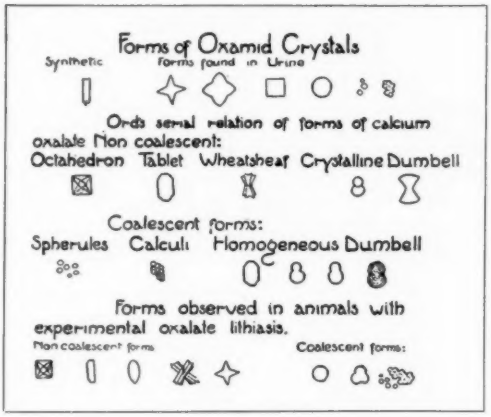

Forms of Oxamid Crystals
Synthetic
Forms found in Urine
Ords serial relation of forms of calcium oxalate Non coalescent:
Octahedron Tablet Wheatsheaf Crystalline Dumbell
Coalescent forms:
Spherules Calculi Homogeneous Dumbell
Forms observed in animals with experimental oxalate lithiasis.
Non coalescent forms
Coalescent forms:

Fig. 1

A diagrammatic sketch of the serial relationship of noncoalescent and coalescent forms of oxamide and of calcium oxalate crystals. W. M. Ord in 1871 recognized the power of colloids *in vitro* to modify the morphology of crystalline matter and traced the relationship of noncoalescent and coalescent varieties of calcium oxalate as shown above. Later he showed with Shattock that the coalescent forms constituted the structural units of calculi as seen microscopically.

2. Hyperexcretion of oxamide, of calcium oxalate and more recently of calcium carbonate, experimentally produced in animals, is associated with agglutination of crystals in an organic framework of colloid to form calculi. This process takes place in the urinary stream, is not confined to the papillae and does not seem to be related

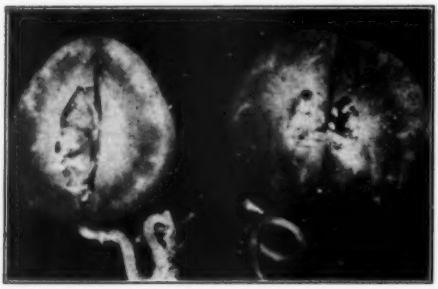


Fig. 2

Bilateral lithiasis in a rabbit fed oxamide daily for seventeen days; larger masses lie behind the free margin where the calices are attached to the renal parenchyma.

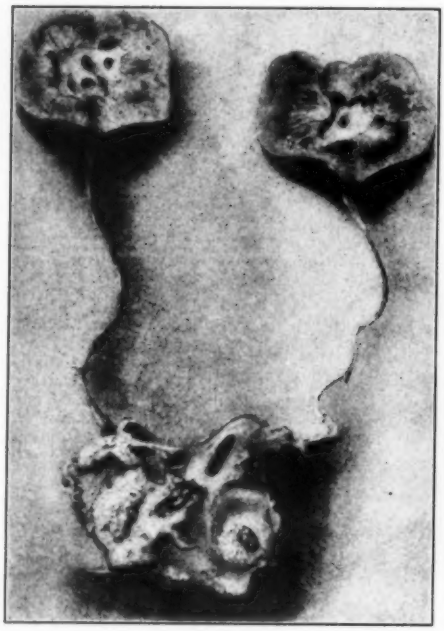


Fig. 3

Calcium oxalate stones in bladder. Result of intense oxaluria produced by injection of normal butyl oxalate and calcium chloride.

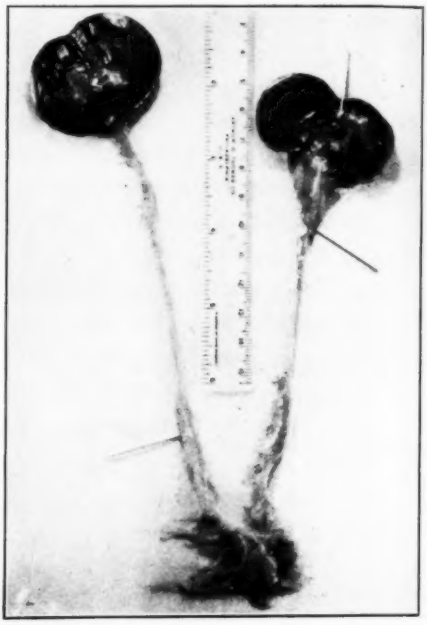


Fig. 4

Calcium carbonate stones in kidneys and ureters of rabbit. Result of feeding 1 gm. calcium carbonate to 2 kg. rabbit daily over 4 months.

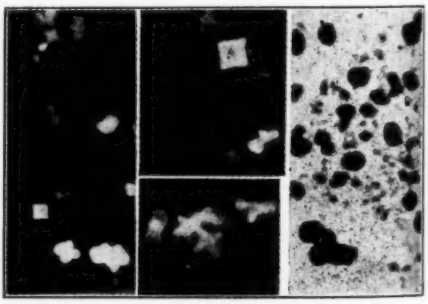
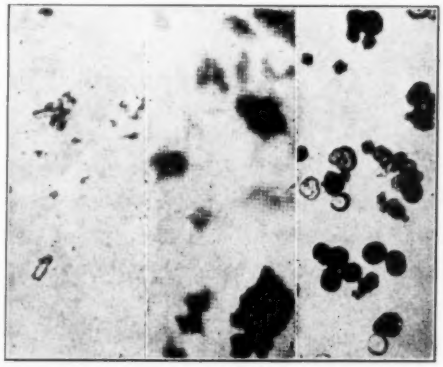


Fig. 5

Oxamide crystals as observed in urine under the influence of the urinary colloids. These crystals have assumed a morphology altogether different from the synthetic form. We can trace the evolution of crystals through noncoalescent crosses, crosses with interbrachial spaces partly filled out, squared forms and coalescent spheroids.

to lime salt impregnation of cells. However, casts of agglutinated crystals are noted at times in the collecting tubules. (Figs. 2, 3, 4).

3. Artificial concrements have been formed in vitro by precipitating fibrin and calcium phosphate simultaneously from the same solution (Schade).
4. Oxamide fed to animals and excreted in the urine undergoes crystalline change to a stone forming type by adsorbing colloid. The process can be repeated in the test tube, where synthetic oxamide dissolved in urine on boiling and reprecipitated on cooling undergoes a change in morphology to spherular stone forming crystals. (Figs. 5, 6).



(A) (B) (C)

Fig. 6

a—Crystals of pure oxamide synthetically prepared; X300.

b—Deposit obtained when synthetic oxamide is dissolved in boiling urine and allowed to precipitate on cooling. The crystals are the developing-cross type; they are pigmented and show marked tendency to fuse into small agglomerations. This sediment is indistinguishable from that in the urine of rabbits fed on oxamide; X300.

c—Oxamide crystals deposited *in vitro* from urine in which the synthetic chemical was dissolved by boiling, showing the perfect smooth sphere and no tendency to fusion; X200.

5. Experimental hyperexcretion of calcium oxalate and carbonate associated with calculus formation shows a similar crystalline morphologic change (Fig. 7). The clinical type of stone which agrees in detail with hyperexcretion calculosis is that associated with hyperparathyroidism. High blood calcium and low phosphorus, a shift of excessive excretion of calcium from the alimentary to the urinary tract, the occurrence of calcium phosphate casts and amorphous spheroidal crystals in the urine, the tendency to bilateral lithiasis, and

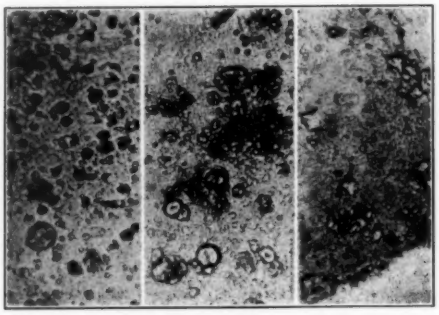


Fig. 7

Small calcium oxalate calculi experimentally produced as in text, crushed on slides to show crystalline elements in structures. Note that the small fusing spheroids constitute the structural units.

finally, the cessation of the stone-forming process when the hyperparathyroidism is corrected with restoration of a normal calcium phosphorus excretion, establish the fact that hyperexcretion of calcium phosphate has been the cause of the stone formation.

The incidence of calculus in association with phosphaturia, oxaluria and uraturia in excessive amounts has not been definitely determined. We do know that stone is frequent in these diseases, but clinical reports as to the quantitative urinary excretion of the salts involved are lacking. However, the impression remains that gouty individuals on excessive urate elimination frequently have ureteral colic. Indeed, in a few instances of recurrent urate calculi, we have found the blood uric acid elevated. It is therefore likely, but not established, let us emphasize, that excretion of phosphate, oxalate and urate may progress quantitatively to the point of crystalline precipitation at a given pH, colloid and salt concentration. These crystals are isolated units as a rule and pass with the urine. However, when the excretion exceeds a certain threshold level, crystalloid and colloid precipitation takes place simultaneously with concrement formation as a result.

6. Cystin and xanthin stones owe their origin to the entrance of foreign water insoluble crystalline matter into the urinary stream by reason of metabolic error. Hence the mechanism of their formation appears to correspond essentially to that of the hyperexcretion type.

7. Fibrin calculi appear to be our only known example of stone resulting from a foreign colloid (fibrinogen) being precipitated simultaneously with lime salts. The clinical cases parallel in some measure Schade's test tube experiment, as in these stones fibrin and calcium salts are found precipitated together.

Again the probability exists, theoretically at least, that colloidal changes may take place in the urine with consequent loss of urinary solution power and precipitation of crystalline matter which is being excreted in amounts normally held in solution or deposited as isolated units. The existence and cause of such colloidal change has not been demonstrated to date, yet such a possibility cannot be excluded from consideration. This concept might explain why some phosphaturias, oxalurias and uraturias escape calculous formation and others do not.

The Crystalline Encrustation Impregnation Mechanism Specific Infection as a Cause of Stone

Stones may arise from the impregnation or encrustation of cells, bacteria, tissues, or foreign bodies with urinary salts. This salt deposition may occur within or upon the cell, within certain layers of tissues, such as in subepithelial plaques (as described by Randall), upon clumps of bacteria or upon any foreign body. The deposition of lime salts in necrobiotic tissues has not been satisfactorily clarified nor will I enter at this time into the many theories which pathologists have advanced to explain the process. However, the scientific establishment of a salt encrustation impregnation mechanism in forming stone rests upon the following facts:

1. Stone may be produced in animals by infection with specific stone-forming bacteria isolated from the urinary tract of patients with rapidly growing or recurrent calculi. This has been demonstrated by Hegar and Magath with proteus, by myself with streptococci, and by Hellstrom and Hryntshak with staphylococci, while Rosenow and Meisser with streptococci from the teeth of such patients reproduced stone in dogs. Hegar and Magath found the bladder mucosa of rabbits to be impregnated with lime salts as the result of infection with the alkaline urea splitting proteus. I likewise noted calcium impregnation of urinary tract epithelium under such conditions after infection with streptococci and could trace

histogenetically the breaking off of particles of this lime-encrusted tissue to grow and form free vesical, ureteral and renal calculi. (Figs. 8, 9).

2. In a series of human kidneys with calculous pyonephrosis, sections of tissue adjacent to stones in calyces when stained with Von Kossa's silver nitrate method for calcium phosphate, show lime impregnated cells and I have been able to trace the histogenesis of stone from this calcified renal epithelium, portions of the calcified material breaking off to form free calculi, or at times remaining attached to the subjacent tissue, the mass growing into the calycal lumen. In histologic detail this process corresponds to that observed in experimental animals with infectious calculosis. (Fig. 10).

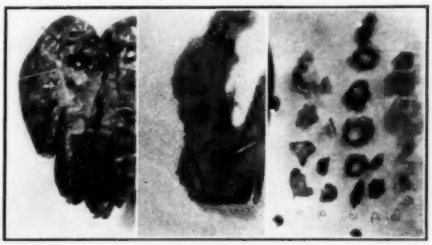
3. Randall has shown that stone frequently arises from subepithelial salt deposition in papillary "milk plaques." This process he feels may not be associated with infection, but its actual cause is as yet indeterminate.

4. Again stone can be produced experimentally in many species of animals by extreme dietary starvation in vitamin A and B, especially the former. The histogenetic study of such calculosis reveals keratinization of urinary epithelium with an intensely alkaline crystalline urine, in consequence of which deposition of lime salts takes place within and upon this effete epithelium. (Osborne, Mendel, Ferry, McCarrison, Fujimake, VanLeersum, Peacock, Higgins, Grossman). Infection appears late as a rule and after the lime salt deposition has begun. The role of infection in producing larger calculi is indeterminate. However, the fundamental picture of lime salt encrustation impregnation mechanism appears again.

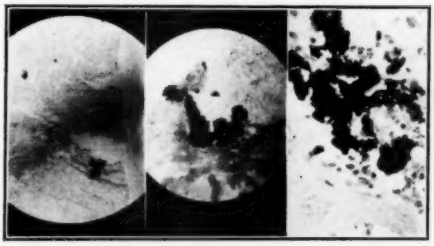
5. The association of calculi, chiefly the carbonate and phosphate variety, with alkaline urea splitting organisms such as the proteus, streptococci and staphylococci is well known. These are the secondary calculi of Albarran in contradistinction to the primary or assumedly aseptic calculi, composed of urates and crystalline phosphates and carbonate, which are more often found in neutral or acid urines. The reproduction of such secondary calculi by intravenous, dental canal and direct vesical infection by different workers with specific bacteria from stone-forming patients, the failure to produce stone with non-specific bacteria, together with the demon-

Fig. 8

Infectious calculosis produced by infection of rabbit's bladder with streptococci from the urine of a stone forming patient. Note encrusted cystitis, dilated ureters and pyonephrosis five weeks after infection.



(A)



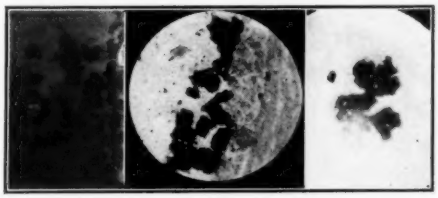
(B)

Fig. 10

Histogenesis of calycal stone in human kidney removed at operation.

a—Areas surrounding calycal stone removed for section and stained by Von Kossa method for calcium.

b—Above areas stained with Von Kossa stain. Lime salt deposition within and upon epithelium, growing into lumen of calyx and breaking off to form free calculi.



(A) (B) (C)

Fig. 9

Histogenesis of infectious lithiasis in rabbits bladder as shown in Fig. 8.

a—Necrobiotic epithelium produced by chemical irritation.

b—Encrusted epithelium breaking off to form calculi.

c—Encrustation of surface cells beginning.

stration of cell impregnation with lime salts both in animal and human urinary tracts, demands that we accept specific bacterial infection as the cause of at least one variety of stone. These calculi are unilateral and affect one site more often than the bilateral stones or those occurring at several sites in the urinary tract which are found when the hyperexcretion mechanism is at fault. They frequently cease to form after removal when drainage and elimination of the infection are established.

6. The clinical occurrence of vitamin deficiency stone is as yet speculative. The geographic incidence of calculus, its relative disappearance in children of today as the result of better dietary, its infrequency in negroes, etc., are explained by the vitamin content of the diet. Photobiometric tests such as that of Jeans are being used to determine ophthalmologic dark adaptation as a measure of vitamin A deficiency. These tests initially seem to support vitamin A deficiency as a factor in stone formation in many instances. Yet the evidence is incomplete and not conclusive. I have discussed elsewhere why I cannot support the vitamin A theory with enthusiasm. Patients with stone for the most part eat a dietary reasonably adequate in vitamin A. Whether or not they absorb it properly and whether or not the relatively slight lack of this vitamin is associated with stone and no other deficiency symptoms, is very questionable.

The Factor of Urinary Reaction

The solution of stone-forming material in urine is maintained by the protective urinary colloids, such as mucin, fibrinogen, chondroitin sulphuric acid, etc., by the quantity of soluble salts and other solids present and also by the temperature, the dilution and the reaction of the urine. Thus urea, a so-called hydrotrophic compound, increases the solubility of calcium oxalate. The relative role of colloids and organic solids in maintaining solubility has recently been challenged and as we have little tangible knowledge of their practical control, I shall not review this controversy. The H-ion concentration, however, is a great factor in maintaining solution and within certain limits determines the composition of the stone-forming material.

Amorphous phosphates, and carbonates and triple phosphates are precipitated in urines of intense alkalinity, whereas the urates, oxalates and crystalline phosphates and carbonates with occasional exceptions

are thrown down from urines of relative neutrality or acidity (oxalates average pH 5.9, urates pH 5.6, phosphates pH 6.2, uric acid pH 6.5) (Maslow).

Certain authors have held alkalinity itself as a cause of alkaline earth stones. The occurrence of such stones in patients on an alkaline ulcer dietary is cited. However, all ranges of pH are noted in normal individuals without stone and the factors of infection or of hyperexcretion would seem more likely causes of lithiasis in such cases. Certainly some factor other than alkalinity is necessary before stone will form.

– Yet by changing the H-ion concentration of the urine the stone forming process may be definitely altered. In infectious alkaline experimental lithiasis, stone will not form if the animal is fed on an acid ash dietary such as oats, while a highly alkaline dietary seems to intensify the process.

The Factor of Urostasis

The clinical and experimental evidence for urostasis as a primary cause of stone is entirely lacking. In maintaining infection and stagnation, however, it is a matter of great moment. When the stone-forming process is active, when lime salts are being deposited by bacterial action on effete cells or when the colloid-crystalloid coagulation of hyperexcretion is present, it is easy to understand how urostasis augments the retention and growth of stony particles. The experimental evidence for this has been cited in other reports.

Hence in the preventive therapy against recurrence of stone, urostasis is perhaps our greatest point of attack. The removal of obstruction occupies a place equally important with the eradication of infections and the administration of diets and drugs.

Other Factors in Genesis of Calculi

Stones associated with fractures and infectious diseases of bones, with injuries to the vertebral column and spinal cord, come up for consideration. Our knowledge concerning their etiology is not exact and time does not permit an account of the theories that have been advanced to explain their incidence. In bone disease a disturbance of the calcium phosphorus excretion is held, not without controversy to be sure, to be the cause. The tendency to bilaterality of such stones, their apparent initial independence of infection, supports the theory of

hyperexcretion as the mechanism at fault. In "osteitis deformans", Goldstein and Abeshouse feel that vitamin A deficiency may explain the increased incidence of calculous disease. In "osteitis fibrosa cystica" increased calcium excretion in association with hyperparathyroidism seems the cause, while in rickets the frequent incidence of lithiasis is explained again as due to an increased calcium phosphorus excretion.

Bacterial clumps encrusted with urinary calculi, i.e., the bacterial nuclei stones, such as have been described by Eisenstadt, Scholl and others, are interesting. Hellstrom has shown staphylococci in layers within the laminations of alkaline calculi. Whether the bacterial clump acts as a foreign body or as a urea splitting agent to precipitate lime salts on effete cells is controversial, although the weight of evidence supports the latter conclusion.

The factors of renal trauma, formation of stones on sutures, in fistulous tracts, in association with tuberculosis and cancer offer material for speculation which for the time must be passed by, as exact evidence of their mechanism of formation is lacking.

From this background, however, we must conclude that stone is not a disease entity. Rather it is a physical manifestation of crystalline matter, i.e., a change in form which results from several physicochemical mechanisms. Two of these mechanisms, viz., the colloid-crystalloid precipitation type as produced by crystalline hyperexcretion and the encrustation-impregnation type produced by specific bacterial action have been established and demonstrated on experimental and clinical grounds. Nevertheless, other mechanisms must yet be determined to explain the manifold aspects which stone disease may assume.

Dissolution of Urinary Calculi

Crowell's dissolution of cystin calculi by urinary alkalinization and Randall's use of phosphoric acid to dissolve small fragments marked the first steps in this line of therapy. The solvent for stone has long been sought. Being impressed with the alkalinity of the urine associated with certain alkaline earth stones, I attempted to shift the urinary reaction to the acid side using dilute nitro-hydrochloric acid, ammonium nitrite and chloride and an acid ash diet. In 1933 I reported with x-ray demonstration partial dissolution of a carbonatic calculus by such urinary acidification, the first instance of its kind. (Fig. 11). Since then I have been successful in causing the disintegration and passage of six alkaline

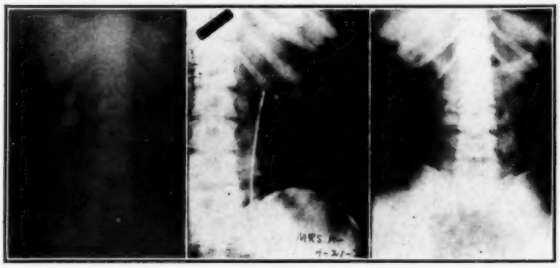


Fig. 11

Large carbonatic calculous pyonephrosis in right kidney treated by nephrectomy. Recurrence in left kidney after thirty days. Streptococcic infection. Reduction in size of calculous mass with two small fragments remaining after thirty days of urinary acidification and pelvic lavage with phosphoric acid.

calculi by urinary acidification, and of two uratic stones by intense urinary alkalinization.

The development of the acid-base diets with addition of vitamin A was popularized by the reports of Higgins and others, so that the method has enjoyed a fair period of trial in the hands of American urologists. Undoubtedly too much was expected of the method, as the results on the whole have been disappointing. The report of Oppenheimer and Pollack from Beer's Clinic is exemplary of the usual failures that have been obtained by this type of therapy when careful statistical tabulation of cases is carried out.

Recently-formed, soft concretions of calcium phosphate and carbonate do frequently disappear on urinary acidification. Dense, well-defined calculi of long standing do not respond. Small stones in calyces in well-draining and well-functioning kidneys remain unaffected for years, as do unimpacted ureteral stones, both of which one would believe to be amenable to such therapy.

In this connection the study of dissolution of surgically removed calculi in weak acids in vitro has been interesting. Most carbonatic and phosphatic stones become soft and disintegrated on their surface, but soon a harder resistant layer is encountered upon which the acid fails to act. We fail to remember the organic colloidal matrix in the stone structure, the latter being resistant to weak acid or alkali as it is composed of irreversible colloidal "gel" in which crystals have become enmeshed in the process of precipitation.

The principle of acid base shift of the urine is of necessity bound to fail even with good renal secretion and proper drainage. The following cases illustrate success and failure of this therapy:

E.G.B., male, aet, 42—Recurrent ureteral calculi of ammonium magnesium phosphate over ten year period. Recurrence stopped by ureteral dilatation and urinary acidification. One small calculus persists in left kidney over nine year period in spite of periods of prolonged urinary acidification and forced vitamin A administration. (Fig. 12).

L.W., nurse, aet, 35—Persistent right ureteral colic. Urinary acidification and vitamin A over two month period. Finally passage of small non-opaque calcium carbonate calculus which easily dissolved in acid in test tube.

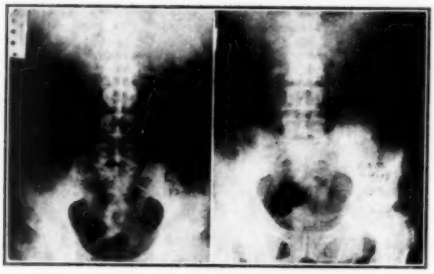


Fig. 12

G.T.B., male, aet, 32—Recurrent phosphatic calculus at left uretero-pelvic juncture after two years. Partial dissolution of stone and passage after two weeks urinary acidification. (Fig. 13).

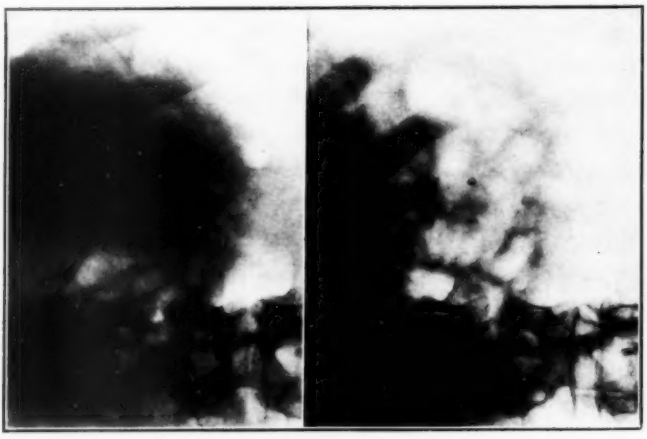


Fig. 13

Mrs. G.T.B. (wife of G.T.B.), female, aet, 30—Stone in right ureter. Good kidney function. Urine alkaline. After four months vitamin A and acidification therapy failure to dissolve. Removal by ureterolithotomy. Phosphate calculus. (Fig. 14).

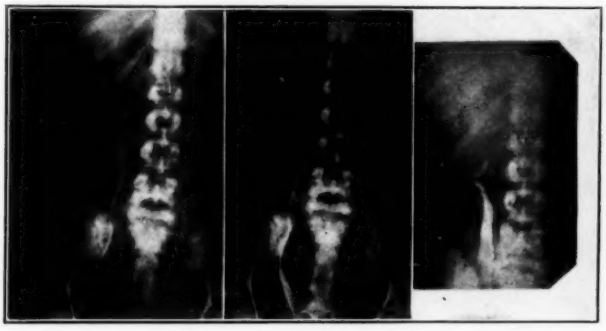


Fig. 14

Mrs. T.O.B., nurse, aet, 30—Recurrent calculus left upper calyx two years after removal of right kidney for calculous pyonephrosis. Observed over a period of six years with frequent ureteral dilatation, vitamin A and acidification of previously alkaline urine. Stone remained stationary in size. Removal by pelviolithotomy. (Fig. 15).

Fig. 15

The direction in which to shift the urinary reaction is not always easy of clinical application. Certain uratic and oxalatic calculi, fibrin types and phosphatic varieties are found with acid and alkaline, with infected and uninfected urines. No single dietary or drug therapy can be expected to give consistent results. Each case must be studied individually. Stones are almost always more or less mixed in chemical composition. This varies with the previous diet, individual metabolic trends and consequent variation in the amount of crystalline stone-

Mrs. O.C.B., female, aet, 50—Bilateral stag horn calculi. Calcium and phosphorus normal in blood. Alkaline urine with proteus infection. Could not acidify. Poor renal function. Death from hemorrhage after operative removal of left calculus. Calcium phosphate in type. (Fig. 16).

Fig. 16

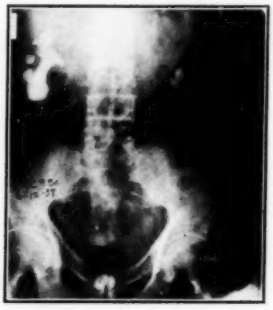


Fig. 17

O.C.B., male, aet, 50, husband of Mrs. O.C.B.—First cousins. Bilateral calculous pyonephrosis. Calcium and phosphorus normal in blood. Alkaline urine with proteus infection. Infection reduced by sulfanilamide and urine acidified by diet and acid therapy pushed to point of tolerance. Vitamin A administered. Operation to date refused. No change in size of calculi. Course progressively downhill with increasing renal insufficiency. (Fig. 17).

forming material excreted. The urinary dilution, the quantity and kind of colloidal matter present, the H-ion concentration, factors constantly changing from hour to hour during the day, come into play. Only within narrow limits can we attempt to control them clinically. Given a patient with calculus we can only conjecture as to the possible relationship of these factors when the stone actually began to form. How to deal with laminated stones where urates, phosphates and oxalates preponderate in different layers, is from the standpoint of shifting the urinary reaction, an unanswerable problem. Hence the purposive dissolution of stone with the present methods is unlikely in an individual case and unless certain circumstances prohibit surgical or cystoscopic removal, dissolution should be attempted only for a short period and with softer types of stone. If no change in size is noticeable within a few weeks, further effort along this line will likely fail and prolonged maintenance of high acidity or alkalinity is not without hazard to the patient's urinary tract.

Prevention of Recurrence of Urinary Calculi

How far are we justified in applying our present knowledge to the important problem of recurrence of stone after surgical removal? I feel that by the application of certain principles which are consistent with our concepts of etiology much of practical value may be accomplished. A system of therapy which I have employed satisfactorily with certain modifications during the past seven years may be outlined as follows:

1. *Remove all stones and fragments as far as possible by surgery or cystoscopy.*

2. *A qualitative chemical analysis of the stone removed should be carried out immediately.*

3. *X-ray should be made immediately and at intervals of six months to one year for several years after operation.*

4. *Seek and correct possibly related metabolic errors.* The blood uric acid, serum calcium and blood phosphorus and phosphatase determinations should be routine observations. Cystinuria should be investigated. If hyperparathyroidism is suspected, x-rays of the bones and other pertinent data are to be obtained.

5. *The diet should be regulated with regard to the chemical composition of the stone.* Dietary regulation assumes two aspects. First, the administration of a diet which will deplete exogenous supply of the stone-forming material, e.g. a low purin diet in uratic calculi, or a low oxalate dietary in oxalatic stone. Second, a dietary such as the acid or alkaline ash type which attempts to change the urinary reaction to the point of maximal urinary solution of the stone-forming chemical. Combinations of the two may be and should be attempted.

As for uratic calculi, the consistency with which these stones are associated with a hyperexcretion of uric acid is not known. However, intense urinary alkalinization is attendant upon disappearance of urate crystals from the urine. Therefore, a low purin alkaline ash diet is theoretically ideal here.

Oxalatic stone presents a problem. Exogenous sources should be excluded by low oxalate dietary. However, as Neville has pointed out, the source of oxaluria is probably endogenous, being associated with vitamin B–D deficiency. Oxaluria may be corrected by administration of these vitamins. While oxalates are precipitated in a wide range of urinary reaction, their solubility is perhaps better at a higher acid range.

Therefore, a high acid ash diet, low in oxalates, and rich in vitamin B and D is to be given.

Phosphate and carbonate stones require a high acid dietary. Control from the standpoint of exogenous sources seems impracticable. Cystin is held in solution in alkaline urines. Hence the basic diet is indicated.

6. *Administer Vitamin A*—The controversial status of vitamin A in lithiasis has been mentioned. Nevertheless the tonic effect of this vitamin on epithelial structures is indisputable and if tolerated by the already much dieted patient it should be given.

7. *Eliminate urinary and focal infection.* Gram stained smears and cultures of the urine from the bladder and each kidney should be made at the initial urologic examination.

Oral antiseptic drugs may aid and the ketogenic diet or mandelic acid therapy may be tried with success. Neoarsphenamine in coccal infections is of value. However, coccal and proteus infections are most resistant and do not consistently respond to any treatment with which I am familiar. Sulfanilamide cautiously used may reduce proteus infection in alkaline urine and after this infection is eliminated urinary acidification may be accomplished when it has previously not been obtainable.

Focal infection should be routinely removed. Dental, tonsillar, prostatic, cervical, and alimentary tract infections demand especial care.

8. *Establish satisfactory renal and ureteral drainage.* In the attack on urostasis I routinely practice periodic postoperative lavage with the free use of indwelling catheters and ureteral dilatation with bulbs. In spite of sharp controversy concerning this procedure, I feel that it is one of our best therapeutic measures in treating any type of chronic non-tuberculous urinary infection. Nephrostomy, suspension of the kidney, removal of vesical neck obstruction are to be carried out when indicated. Lavage with phosphoric acid in 1 to 2 per cent solution may dissolve encrustation, sand, or minute calculi. The dilated ureter may afford passage to small concretions. Sacrifice the offending kidney only as a last resort.

9. *Shift the urinary reaction to the range which will best keep the stone-forming crystals in solution.* This feature has been previously dealt with. At the outset it is important to determine the H-ion concentration several times daily. The urine from each kidney should be separately studied with indwelling catheters. The patient should be instructed to make his own H-ion determination either with a LaMotte or similar

indicator or with methyl red, nitrazene, or chlorphenol red paper. There is a potential danger in keeping the urine at an intensely acid or alkaline range over a long period of time. Systemic acidosis may be produced by too large or too long continued dosage of acid drugs and even nephritis can occur. For this reason, patients on such a regimen should be under constant observation by an understanding urologist who is familiar with this type of work. Chute has called attention to the fact that ammonium salts may actually form a source of food for urea splitting organisms if urinary acidity is not obtained and that urinary acidification will increase the elimination of calcium salts in the urine. Such calcium hyperexcretion may thus theoretically promote the growth of stone.

10. Patients with fractures, infections or other disease of bone, those with spinal cord lesions, renal trauma, or patients long bed-ridden should have their urine kept acid by diet and drugs and furnished ample vitamins as a prophylaxis against stone.

In 1933 I reported sixteen cases of rapidly recurrent calculi which had had their cycle of recurrence of from one to nine years permanently broken by the use of such measures. Since that time numerous similar cases have been treated successfully by myself and others.

The application of these principles is not easy, and requires an unusual degree of care as to detail on the part of the urologist and the utmost in cooperation on the part of the patient. Certain cases of rapidly recurrent calculi are baffling and at times impossible to correct. Yet we are reducing recurrence according to statistical information to a lower percentage level each year.

Conclusion

Thus I have attempted to present to you the facts known regarding the etiology and prevention of urinary lithiasis. Admittedly the story is long and tangled. Nevertheless present day concepts give us a working basis, a point from which to start that was not existent twenty years ago. Scientific knowledge progresses by a process of evolution in which many investigators take part. With the intense interest at present being shown in this problem in many centers by earnest workers, I feel that it is not too much to prophesy that within a few years much will be added to give us a clearer understanding of this most interesting clinical phenomenon, stone in the urinary tract.

MEASURES SUGGESTED IN PREVENTIVE THERAPY OF RECURRENCE OF URINARY CALCULI

With Comments on the Treatment of Urinary Infections

Stones should be removed surgically or cystoscopically when possible. Dissolution of large dense calculi unlikely with present methods.

A. Chemical analysis of stone removed.

A SIMPLE METHOD FOR THE QUALITATIVE ANALYSIS OF URINARY CALCULI

(Modified from Hawk and Bergeim—Physiologic Chemistry, and Hammarsten-Lehrbuch der Phys. Chem.) Domanski—Jr. Urol. Mar. 1937.

Each of the concentric layers of the calculus must be subjected to separate analysis. Material for examination is obtained by sawing the calculus carefully thru the nucleus, then separating the layers, or by scraping off from each layer (without separating the layers) enough powder to conduct the examination as outlined below. Seek nucleus separately with care. Study microscopically for organized organic matter (cells, bacteria) or foreign body.

On Heating the Powder on Platinum Foil, it*						
Does burn	Without flame	The powder gives the murexide test.**	The powder when treated with KOH gives***	No Noticeable Ammonia Reaction Add conc. HNO_3 to powder—No gas evolved.	Uric acid.
				Strong Ammonia Reaction Add conc. HNO_3 to powder—Evolution of gas (oxides of nitrogen).	Urates (ammonium, calcium, magnesium)
		Does not give murexide test.** The powder dissolves in nitric acid without effervescence. The dried yellow residue becomes orange with alkali, beautiful red on warming.			Xanthine.
	With flame	Flame pale blue, burns a short time. Peculiar sharp odor. The powder dissolves in ammonia, and six-sided plates separate on the spontaneous evaporation of the ammonia.			Cystine.
		Flame yellow, pale, continuous. Odor of resin or shellac on burning. Powder soluble in alcohol and ether.			Urostealith
		Flame yellow, continuous. Odor of burnt feathers. Insoluble in alcohol and ether. Soluble in potassium hydroxide with heat. Precipitated herefrom by acetic acid and generation of hydrogen sulphide.			Fibrin
Does not burn	The powder when treated with HCl	Does not effervesce		Effervesces	Calcium carbonate.
			The powder gently heated, then treated with HCl	Effervesces Filter—Make alkaline to litimus with 16% NH_4OH sol.—Then just acid with 5% acetic acid—Let stand 1 hour—centrifuge and examine for crystals of calcium oxalate:—or treat sediment with N/ H_2SO_4, heat and add drop 0.01 N-$KMNO_4$. Decolorization of permanganate indicates calcium oxalate.	Calcium oxalate.
			The powder when moistened with a little KOH	No ammonia or, at least, only traces of ammonia. Powder dissolves in acetic acid or HCl. This solution is precipitated by ammonia (amorphous precipitate).	Bone-earth (magnesium and calcium phosphate).
				Abundant ammonia. The powder dissolves in acetic acid or HCl. This solution gives a crystalline precipitate with ammonia.	"Triple phosphate" (mixed with unknown amount of earthy phosphate)

*Flame test frequently imperfect with small amounts.

**Murexide Test

To a small amount of the powder in a small evaporating dish add 2-3 drops of concentrated nitric acid. Evaporate to dryness over a very low flame or water bath. A red or yellowish residue remains which turns purplish red after cooling the dish and adding a few drops of very dilute ammonium hydroxide. The color is due to the formation of murexide.

***KOH frequently fails to liberate appreciable ammonia.

Most stones are mixed in composition.

Rapidly recurrent stones tend to be pure and relatively unmixed and of the same composition as their predecessors.

B. **Blood chemistry studies—**

Blood uric acid—serum calcium—blood phosphorus. (Repeat several times.)

C. **Uratic calculi—Low purine diet*—**

Intense alkalinization of urine.

Calcium oxalate calculi—

Low oxalate dietary* Intense acidification of urine. Give Vitamins B and D to decrease oxaluria.

Calcium oxalate is precipitated in a wide range of urinary reaction. Best solution is maintained at pH 5.2, poorest at pH 6.1 (Maslow). This is most difficult stone to dissolve or to control by urinary reaction.

Calcium carbonate and calcium or ammonium magnesium phosphate calculi.

Low phosphate dietary.* (Especially avoid milk and dairy products. Probably high acid ash diet better).

Intense acidification of urine. (pH 4 to 5).

Cystin calculi—

Intense alkalinization of urine.

*An excellent series of diets are listed in an article by Grant and Simpson—Southern Medical Journal—July, 1930. Also consult Barborka, Treatment by Diet, Lippincott, 1934.

D. To acidify urine—*ACID ASH DIET*—(see next page).

Dilute nitrohydrochloric acid (aqua regia).

℞ Conc. nitrohydrochloric acid ..... 10 cc.
Distilled water q. s. ..... 100 cc.

Sig: Take 1 drachm in 1 glass water q. 1 to 2 hrs. to tolerance. Sip through tube and rinse mouth with sodium bicarbonate solution after taking. Care not to swallow bicarbonate solution.

Or Use *ACID DIURETIC MIST.*

℞ Ammonium benzoate .....Dr. II
Ammonium chloride .....Dr. III
Ammonium nitrate .....Dr. III
Saccharose .....Oz. IV
Elixir of Lactated Pepsin q. s. .....Oz. VIII

N. B.—Mix in mortar to syrup.

Sig: Drachms one to two in glassful water every one to two hours unless nauseated.

Each drachm contains 0.5 gm. of acidifying drug.

This syrup is usually well tolerated and has been found the best urinary acidifier in our experience. It may be used together with—

Enteric coated tablets—Ammonium Chloride—6 to 10 gms. daily

Enteric coated tablets—Ammonium Nitrate—6 to 10 gms. daily

Watch stool to be sure enteric coated tablets are absorbed.

The use of the acid diuretic mixture, dilute aqua regia, enteric coated tablets, and acid ash diet singly or simultaneously has generally been well enough tolerated to render acid resistant urinary alkalinity. If patient is nauseated omit one or two doses and continue. When 8 to 10 gm. acidifying drug are exceeded in 24 hours watch for systemic acidosis. Certain types of urea splitting organisms, e.g., proteus and some staphylococci defy urinary acidification. Acid urine is possibly secreted, but is at once alkalinized by bacterial action.

LACTIC OR HYDROCHLORIC ACID MILK (10 to 60 drops of lactic or dilute HCl to 6 oz. boiled milk)—1 glass 4 times or more daily. Useful in infants and children.

E. To alkalinize urine—*ALKALINE ASH DIET*—see next page.

ALKALINE DIURETIC MIST.

℞ Kali citratis .....Oz. I
Sodii bircarbonatis .....Dr. IV
Syr. Orange .....Oz. IV
Aquae Dist. q. s. .....Oz. VIII

Sig: Drachms III in water a.c. and h.s.

Magnesia, potassium citrate or acetate, sodium bicarbonate in suitable prescription.

For H-ion Determination Use Indicator with Color Card such as LaMotte Duplex Indicator (LaMotte Chem. Products Co., Baltimore).
or Use Methyl Red Paper { Red—pH below 5.5; Yellow—pH above 5.5. (approx.)
Columbia # 2x1 }
or Nitrazene Paper { Green—pH above 5.2.
or 0.04 percent chlorphenol red—1 drop to 20 drops urine { Red—pH 5.2; Pink—pH 5.5 to 5.8.
— Patient May Be Taught To Use These —

F. **TO TREAT THE URINARY TRACT INFECTION—**

SMEARS AND CULTURES at Initial Urologic Examination.

Study voided and catheterized bladder urine, catheterized ureteral specimens from each kidney, determining pH on usual dietary.

Differentiate infectious organisms by laboratory methods. (Gram stain simple and useful.)

NEOARSPHENAMINE—0.2 gm. intravenously followed in 5 to 7 days by 0.3 gm.

Frequently of value in staphylococcus and streptococcus fecalis. Do not continue if first two doses show no improvement. Use cautiously in acute infections and with renal insufficiency.

METHENAMINE—Keep urinary reaction below pH 5.6. Push dosage to tolerance 4 to 8 gm. daily. Watch urine for increase in red cells or casts. Do not continue large doses over long period. Drop maintenance dose to 3 to 4 gm. daily. If not effective after several days do not continue. If given intravenously calculate amount in total daily dosage.

ACRIFLAVINE—CAPROKOL—AZO DYES (Pyridium, Serenium, etc.). Seldom sterilize urine, but good bacteriostatics and reduce infection.

KETOGENIC DIET—References—Clark, A. L. J. A. M. A. 107: 1280-1284-1936. Nesbit, R. M. J. A. M. A. 105: 1183-1184-1935.

Not well tolerated in many patients. Used less frequently now as mandelic acid in most instances affects same organisms more successfully and is better tolerated. Bacillary and streptococcus fecalis infections respond best, coccal infections poorly except at times in lower urinary tract.

MANDELIC ACID—Has largely replaced ketogenic diet. Keep urinary concentration high by restricting fluids to 1000 to 1200 cc. daily (except in acute cases). Keep pH by acid-ash diet and drugs at pH 5.2.

Give 12 gm. mandelic acid daily to adults (as sodium mandelate or ammonium mandelate). Infants and children according to age. Do not continue over two or three weeks and examine urine carefully for appearance or increase of red cells and casts. In cases of renal insufficiency take care not to produce acidosis. Watch for nausea, vomiting, hyperpnoea and check CO_2 combining power of blood.

SULFANILAMIDE—In urinary tract effective for bacilli including proteus. Does not affect cocci so well. Streptococcus fecalis does not respond.

Active (probably most active) in alkaline urine. Keep pH at 7.5 or higher. Develops bactericidal urine in renal insufficiency. At present oral administration appears equally or more effective than intramuscular or intravenous routes. Secreted in poor concentration in prostatic secretion, but very effective in prostatic infection. Dosage not standardized —Start with 60 to 80 grains daily in four doses. Reduce to 40 grains daily after 2 or 3 days.

Watch tolerance of patient and for many bizarre untoward reactions—Progressive cyanosis, hemoglobinuria, hematuria, hyperpyrexia, leucopenia, agranulocystosis, erythraemia, dermatitis, anemia, jaundice and retinitis indicate discontinuance of drug. Usually prompt recovery from toxic symptoms ensues. Do not give any type of sulphates and especially avoid magnesium sulphate during sulfanilamide administration. Watch patient daily.

REDUCE FOCAL INFECTIONS—teeth—tonsils—prostate—cervix—alimentary tract.

SURGICAL DRAINAGE—Nephrostomy—Seminal Vesiculotomy—Cystostomy—Removal of prostatic obstructions—Suspension of kidney, etc.—when indicated.

UROLOGIC DRAINAGE—Indwelling catheters—Periodic cystoscopic, ureteral dilatation. Dilatation of small calibered urethras. Valuable measures if applied gently and increasing size of dilator gradually. Avoid trauma.

Lavage with 1 to 2% phosphoric acid, etc. Continuous irrigation with acids by any method is not tolerated by most patients and may provoke severe reactions. Of value chiefly in post-operative effort to prevent recurrence of stone.

SUMMARY:

Surgical removal of stone usually indicated when possible. Adjust urinary reaction in accordance with chemistry of stone.

Correct metabolic error—hyperparathyroidism, uric acid, oxalate, phosphate hyperexcretion. Reduce infection. For coccal infections use neoarsphenamine and methenamine. For bacillary infections and streptococcus fecalis use urinary acidification and mandelic acid. In alkaline bacillary infections use sulfanilamide. Remove focal infection. Establish drainage.

Patients with bone disease (fractures, infections, tumors, osteitis deformans, osteitis fibrosa cystica); patients with spinal cord injuries or patients long bedridden—keep urine at acid range (pH 5 to 5.2) as prophylaxis against stone.

G. Increase Vitamin A Intake—Sources—Cod liver oil—Haliver oil—Carotene (Provitamin A).

FOODS—

APRICOTS
BEEF LIVER
Beef Fat
BUTTER
Bananas
Cantaloupe
CHARD
CHEESE (Am. or Swiss)
CREAM
EGG YOLK
Kidneys
Milk
Oranges
Oysters
Peaches
Pineapples
Prunes
Tomatoes

Vegetables with green or yellow pigment, as

Asparagus
Beans, green
Cabbage
CARROTS
Corn (yellow)
CRESS
LETTUCE
PEAS (green)
Peppers
Pumpkins (yellow)
Sweet Potatoes
Squash
SPINACH
TURNIP (tops)

ACID-ASH DIET

(Expressed in cc. Normal reagent per 100 gm. food)

This diet is deficient in Vitamin C. For this reason Vitamin C vegetables of low alkaline-ash content may be added periodically if the patient is on the diet for a long time.

Egg Yolk	27.	Pork, lean	10.	Crackers, soda	8.3	Bread (rye)	4.9
Oysters	15.1	Veal, loin	9.8	Pork chops	8.	Corn Meal	4.9
Macaroni	14.3	Ham, smoked	9.7	Walnuts	7.8	Peanuts	3.9
Shredded Wheat	12.2	Sponge Cake	9.0	Bread, whole wheat	7.3	Corn, green	1.8
Whole Wheat	12.	White Flour	9.0	Bread, white	7.1	Cranberries, Plums, including Prunes	
Oatmeal	12.	Beef, ribs, lean	9.6	Perch	6.3		
Sardines	11.3	Mutton, leg	9.6	Corn, (dry)	5.9		
Eggs, whole	11.	Soy bean Meal	9.5	Cheese, Cheddar- (American)	5.4	NEUTRAL	
Beef, porterhouse steak	10.9	Rice	9.3	Egg White	5.2	Tapioca, Lard	
Chicken	10.7	Halibut, fresh	9.3	Lentils	5.1	Butter, Sugar	
Salmon, canned	10.7	Flour, white	9.0	Swiss Cheese	5.	Cream, Cornstarch	
Barley, pearl	10.4	Trout, salmon	8.8	Bacon	5.	Oil	
Beef Liver	10.5	Cod fish	8.4				

ALKALINE-ASH DIET

(Expressed in cc. of Normal reagent per 100 gm. food)

Molasses	56.	Citron	9.6	Bananas—C	5.6	Raspberries—C	3.8
Olives	45.6	Rutabagas—C	8.5	Oranges—C	5.6	Apples—C	3.7
Dried Figs	32.9	Rhubarb—C	8.5	Tomatoes—C	5.6	Pears, fresh	3.6
Spinach	27.0	Cucumbers—C	7.9	Beans, fresh string	5.4	Radishes—C	2.9
Raisins	23.6	Celery—C	7.8	Condensed Milk	5.2	Watermelon—C	2.7
Beans, dried	18.	Cantaloupe—C	7.5	Evaporated Milk	5.3	Turnips—C	2.7
Dried Milk	18.	Lettuce—C	7.4	Cauliflower—C	5.	Milk, whole, raw	2.5
Chard	15.8	Potatoes, white—C	7.	Lemons—C	5.	Buttermilk	2.2
Beans, fresh lima	14.	Cocoanut	7.	Peas (dry)	5.	Onions—C	1.5
Almonds	12.3	Pineapples, fresh—C	6.8	Peaches, fresh—C	5.	Pumpkins—C	1.5
Parsnips	12.	Sweet Potatoes—C	6.7	Chestnuts	5.	Peas, fresh—C	1.3
Dates	11.	Cabbage—C	6.	Cherries—C	4.5	Asparagus—C	0.8
Beets, fresh	10.9	Baked Beans	6.	Mushrooms	4.	Grapefruit—C	alk.
Carrots—C	10.8	Apricots	6.	Grape Juice	4.	Ice Cream	0.2
Figs	10.						

C signifies high Vitamin C content.

SOFT ACID-ASH DIET

May have the following foods:

EGGS (poached, soft boiled, souffle, egg custard, shirred, creamed, omelet, scrambled).
MACARONI (creamed, buttered or cooked in chicken stock).
COOKED CEREALS (rice and grits may be served as vegetables or cereals, and oatmeal, cream of wheat, farina, and wheatena, also cornmeal as mush).
CRACKERS.
BREAD (whole wheat, rye and white).
CORN (green or canned, either very tender or run through sieve to remove outer skin).
DESSERTS (custard, rice puddings, tapioca custard, bread puddings—made with eggs and one-half milk and one-half 20% cream).
CHICKEN (stewed, creamed or baked).

Later may have:

Fresh halibut boiled, broiled or baked.
Fresh trout boiled, broiled or baked.
FRUITS (cranberries, plums (cooked) and prunes (may be combined with eggs as whips or souffles).
NEUTRAL FOODS (cream, butter, tapioca, sugar, cornstarch).

SAMPLE MENU FOR DAY:

BREAKFAST	LUNCH	DINNER
Prunes with cream. Oatmeal, shredded wheat with cream. Poached egg on toast. Toast with butter. Coffee or tea with cream and sugar.	Cream of chicken soup with crackers. Egg omelet. Buttered grits. Stale muffins (toasted with butter). Prune whip (made with stiffly beaten egg white, pureed prunes and sugar). Coffee or tea with cream and sugar.	Bouillon with toasted crackers. Stewed chicken with gravy. Steamed rice. Stewed corn. Toast with butter. Baked chocolate custard. Coffee or tea with cream and sugar.

SOFT ALKALINE-ASH DIET

FRUITS ALLOWED—(all fruits on list)—
Orange juice, pineapple juice, grapefruit juice, tomato juice, peach juice, apricot juice, pear juice.
Baked apple without skin, baked pear without skin, fresh or canned applesauce, canned peaches, pears, apricots, Royal Anne cherries.
VEGETABLES on alkaline list—
All vegetables must be **strained.** Carrots, peas, lima beans, butter beans, string beans, tomatoes, asparagus, spinach, beets, squash, baked potato, or mashed potato.
MILK AND MILK PRODUCTS ALLOWED—
Sweet or buttermilk, cottage cheese, cream, butter.
Any ice cream without solid fruits or nuts.
Chocolate milk or hot chocolate.
BREADS ALLOWED—
Toast (white or brown) **NOT MORE THAN ONE AND ONE-HALF SLICES EACH DAY.**
EGGS—Do not eat more than **ONE** egg a day.
DESSERTS (BESIDES FRUITS) ALLOWED—Simple puddings made with any of the allowed fruits—Baked custards, tapioca puddings.
COFFEE AND TEA—MAY BE TAKEN AS DESIRED.
Sugar, salt and pepper as desired.

SAMPLE MENU FOR DAY:

BREAKFAST	LUNCH	DINNER
Any allowed fruit or fruit juice. One egg. Milk. Coffee or tea. ½ slice bread (toasted).	Cream or vegetable soup. Baked potato. Vegetable purees. ½ slice toasted bread. Milk. Allowed fruit or dessert or both.	Fruit cup. Mashed potato. Vegetable purees. ½ slice toast. Milk. Dessert.

NOTES ON SOFT ALKALINE-ASH DIET:

In keeping a diet alkaline—eggs, which are one of our most valuable sources of protein in the soft diet must be very limited, so in order to keep the body built up a great deal of milk should be consumed.
The patient should take at least 1½ quarts of milk each day. This may be used in soups, specially-prepared drinks, or may be taken plain.
Notice that none of the foods allowed are limited in amounts except eggs and toast. These are limited because they contain acid properties.

RECENT ACCESSIONS TO THE LIBRARY

"Possession does not imply approval"

Bailey, E. H. S. & Cady, H. P. *A laboratory guide to the study of qualitative analysis.* 10 ed.
Phil., Blakiston, [1937], 322 p.

Barnhill, J. F. *Surgical anatomy of the head and neck.*
Balt., Wood, 1937, 921 p.

Bertwistle, A. P. *The rôle of chemiotaxis in bone growth.*
London, Kimpton, 1937, 59 p.

Bivin, G. D. & Klinger, M. P. *Pseudocyesis.*
Bloomington, Ind., Principia Press, 1937, 265 p.

Blanchard, C. E. *A handbook of ambulant proctology.*
Youngstown, O., Medical Success Press, 1937, 304 p.

Bloom, C. J. *The care and feeding of babies in warm climates.*
New Orleans, Pelican Pub. Co., [1937], 358 p.

van Bogaert, L.; Scherer, H. J. & Epstein, E. *Une forme cérébrale de la cholestérinose généralisée.*
Paris, Masson, 1937, 182 p.

Bourne, A. W. *Synopsis of obstetrics and gynaecology.* 7 ed.
Bristol, Wright, 1937, 452 p.

Brown, C. A. *Life of John Keats.*
London, Oxford Univ. Press, 1937, 129 p.

Burrell, L. S. T. *Recent advances in pulmonary tuberculosis.* 3 ed.
London, Churchill, 1937, 320 p.

Chiray, M. M. & Pavel, I. *La vésicule biliaire et ses voies d'excrétion.* 2 éd.
Paris, Masson, 1936, 863 p.

Cranfill, J. B. *From memory.*
Nashville, Boardman Press, [1937], 281 p.

Curie, E. *Madame Curie, a biography.*
Garden City, Doubleday, 1937, 393 p.

Davis, M. M. *Public medical services.*
Chic., Univ. of Chic. Press, [1937], 170 p.

Dressler, W. *Klinische Elektrokardiographie.* 4 Aufl.
Berlin, Urban, 1937, 180 p.

Fels, E. *Das Hormon des Corpus luteum.*
Leipzig, Deuticke, 1937, 169 p.

Fishbein, M. *Syphilis; the next great plague to go.*
Phil., McKay, 1937, 70 p.

Flick, L. F. *Tuberculosis.*
Phil., [Author], 1937, 330 p.

Franklin, K. J. *A monograph on veins.*
Springfield, Ill., Thomas, 1937, 410 p.

Frolov, Y. P. *Pavlov and his school; the theory of conditioned reflexes.*
London, Paul, 1937, 291 p.

Gaehtgens, G. *Der Vitaminhaushalt in der Schwangerschaft.*
Dresden, Steinkopff, 1937, 161 p.

Gesell, A. L. & Ilg, F. L. *Feeding behavior of infants.*
Phil., Lippincott, [1937], 201 p.

Glasstone, S. *The electrochemistry of solutions.* 2 ed.
London, Methuen, [1937], 551 p.

Goldsmith, M. L. *Florence Nightingale; the woman and the legend.*
London, Hodder, [1937], 320 p.

Harvey, W. C. & Hill, H. *Milk products.*
London, Lewis, 1937, 387 p.

Hertzler, A. E. *Surgical pathology of the diseases of the neck.*
Phil., Lippincott, [1937], 237 p.

Hinside, L. E. *Concepts and problems of psychotherapy.*
N. Y., Columbia Univ. Press, 1937, 199 p.

Holman, E. *Arteriovenous aneurysm.*
N. Y., Macmillan, 1937, 244 p.

Hoyland, J. S. *That inferiority feeling.*
London, Allen, [1937], 256 p.

Hutchison, R. *The elements of medical treatment.* 3 ed.
Bristol, Wright, 1937, 194 p.

International (2) Congress of Medical Advisers for Athletes, Berlin, 1936. *Verhandlungsbericht.*
Leipzig, Thieme, 1937, 415 p.

International Society for Microbiology. International (2) congress for microbiology, London, 1936. *Report of proceedings.*
London, [Harrison], 1937, 579 p.

Kerr, J. M. M. *Operative obstetrics.* 4 ed.
London, Baillière, 1937, 847 p.

Langdale, A. B. *Phineas Fletcher, man of letters, science and divinity.*
N. Y., Columbia Univ. Press, 1937, 230 p.

Levinson, C. A. *The examining dentist in food hazard cases.*
Boston, Author, 1937, 58 p.

Lewis, (Sir) T. *Clinical electrocardiography.* 6 ed.
London, Shaw, 1937, 128 p.

Leys, A. *Recherches sur les eaux polluées.*
Paris, Baillière, 1936, 111 p.

Lhotte, C. & Dupeyrat, E. *Révélations sur la santé des jeunes travailleuses.*
Paris, Éditions Spes, [1936], 191 p.

Ling, T. M. *Recent advances in industrial hygiene and medicine.*
London, Churchill, 1937, 212 p.

MacCracken, W. B. *Use your own eyes.*
Berkeley, Cal., Author, 1937, 241 p.

McKay, W. J. S. *The evolution of the endurance, speed and staying power of the racehorse.*
London, Hutchinson, [1937], 319 p.

McNally, W. D. *Toxicology.*
Chic., Industrial Medicine, 1937, 1022 p.

Marshall, H. E. *Dorothea Dix, forgotten Samaritan.*
Chapel Hill, Univ. of North Carolina Press, 1937, 298 p.

Mathey-Cornat, R. *Radiothérapie gynécologique.*
Paris, Masson, 1936, 369 p.

Mitchell, J. P. *Anatomy and physiology, and causes of disease.*
London, Baillière, 1937, 215 p.

Murva, H. G. *Dix ans chez les dentistes.*
Paris, Bondaz, [1936], 219 p.

Newsholme, H. P. *Christian ethics and social health.*
London, Heritage, [1937], 155 p.

Neymann, C. A. *Artificial fever produced by physical means; its development and application.*
Sprinfield, Ill., Thomas, [1937], 294 p.

Oosterhuis, R. A. B. *Paracelsus en Hahnemann; een renaissance der geneeskunst.*
Leiden, Sijthoff, [1937], 300 p.

Page, I. H. *Chemistry of the brain.*
Springfield, Ill., Thomas, (1937), 444 p.

Pattee, A. F. *Practical dietetics.* 21 ed.
Mount Vernon, N. Y., Pattee, 1937, 868 p.

Pekin, L. B. *Darwin.*
London, Woolf, 1937, 78 p.

Pinsent, (Dame) E. F. (Parker). *The mental health services in Oxford City, Oxfordshire and Berkshire.*
Oxford, Barnett House, 1937, 87 p.

Raw, N. *The control of bovine tuberculosis in man.*
London, Baillière, 1937, 128 p.

Rudolph, J. A. *Allergy; its practical application.*
Phil., Dorrance, [1937], 224 p.

Schlesinger, B. *Einführung in die Ventrikulographie.*
Berlin, Urban, 1937, 246 p.

Science museum, London. *Pure chemistry.*
London, H. M. Sta. Off., 1937, 2 pts. in 1 v.

Sears, W. G. *Vade mecum of medical treatment.*
Balt., Wood. 1937, 368 p.

Smith, E. A. *A manual of dental metallurgy.* 5 ed.
London, Churchill, 1937, 320 p.

Solomon, C. *The traffic in health.*
N. Y., Navarre Pub. Co., [1937], 393 p.

Souttar, H. S. *The art of surgery.* 3 ed.
London, Heinemann, 1937, 630 p.

Steele, (Mrs.) K. M. *Psychiatric nursing.*
Phil., Davis, 1937, 370 p.

Stephens, J. W. W. *Blackwater fever.*
[Liverpool], Univ. Press of Liverpool, 1937, 727 p.

Stewart, (Sir) J. P. *The diagnosis of nervous diseases.* 8 ed.
London, Arnold, [1937], 842 p.

Todd, A. T. *Treatment of some chronic and 'incurable' diseases.*
Bristol, Wright, 1937, 203 p.

Todd, T. W. *Atlas of skeletal maturation.*
St. Louis, Mosby, 1937, 202 p.

Toumanoff, C. *L'anophélisme en Extrême-Orient.*
Paris, Masson, 1936, 434 p.

Vallery-Radot, J. L. P. *Les grands problèmes de la médecine contemporaine.* [Paris], Flammarion, [1936], 252 p.

Wakeley, C. P. G. & Hunter, J. B. *Rose & Carless' manual of surgery.* 15 ed. London, Baillière, 1937, 2 v.

Williams, L. L. B. *Minor maladies and their treatment.* 7 ed. London, Baillière, 1937, 439 p.

Wilson, J. St. G. *Pre-natal and post-natal management.* London, Arnold, 1937, 206 p.

Wolberg, L. R. *The psychology of eating.* London, Harrap, [1937], 321 p.

PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

JANUARY 6—*The New York Academy of Medicine Annual Meeting.* Executive Session—a] Reading of the minutes; b] Presentation of diplomas. ¶ Presentation of annual reports (read by title), The Council, The Trustees, The Treasurer, Committees. ¶ Report of the Fund Raising Committee, Shepard Krech. ¶ Address of the President, James Alexander Miller, The significance of The New York Academy of Medicine. ¶ Report on election of members.

JANUARY 20—*The Harvey Society in affiliation with The New York Academy of Medicine.* The fourth Harvey lecture, "Transfers of Water and Solutes in the Body," John P. Peters, Professor of Medicine, Yale University.

SECTION MEETINGS

JANUARY 4—*Dermatology and Syphilology.* Reading of the minutes. ¶ Presentation of cases—a] Vanderbilt Clinic, College of Physicians and Surgeons; b] Miscellaneous cases. ¶ Discussion of selected cases. ¶ Executive session.

JANUARY 7—*Surgery.* ¶ Reading of the minutes. ¶ Presentation of cases—Two cases to illustrate each paper of the evening. ¶ Papers of the evening—a] Surgery in the treatment of advanced cancer of the lip, Hayes E. Martin; Discussion, Jerome P. Webster; b] Common carotid artery ligation in head and neck cancer, William L. Watson; Discussion, John M. Hanford; c] The use of the actual cautery in the treatment of carcinomas of the head and neck, William S. MacComb (by invitation); Discussion, William F. MacFee. ¶ General discussion. ¶ Executive session.

JANUARY 11—*Combined Meeting, Section of Neurology and Psychiatry and The New York Neurological Society.* Presentation of cases—Two cases demonstrating allergic reactions in the central nervous system, Irving Pardee. ¶ Papers of the evening—a] Allergy and its effect on the central nervous system, Foster Kennedy; Discussion, Angus Frantz, Robert A. Cooke, Israel Wechsler; b] Sulfanilamide in the treatment of acute infections of the central nervous system, Josephine B. Neal; Discussion, Emanuel Appelbaum, Clarence C. Hare. ¶ Executive session.

JANUARY 12—*Historical and Cultural Medicine.* Reading of the minutes. ¶ Papers of the evening—a] Sidelights on the history of medicine in Spain and Portugal, Harry Friedenwald, Baltimore (by invitation); b] Hieronymus Münzer and other Fifteenth Century Bibliophiles, E. P. Goldschmidt, London (by invitation). ¶ General discussion. ¶ Executive session.

JANUARY 13—*Pediatrics.* Program presented by members of the Department of Pediatrics of the University of Pennsylvania Medical College. ¶ Papers of the evening—a] Curd size and curd tension of milk, Irving J. Wolman (by invitation), Leslie A. Chambers (by invitation); Discussion, Logan T. Wilson (by invitation), Plainsboro, N. J.; b] Some observations on hypertension in acute glomerulonephritis, Mitchell I. Rubin (by invitation), Milton Rapoport (by invitation); Discussion, John D. Lyttle; c] The effect of the maternal diet upon resistance to infection, Charles F. Church (by invitation); Discussion, Leslie T. Webster (by invitation); d] The velocity of spread of nasopharyngeal infection, W. F. Wells (by invitation), M. Wells (by invitation); e] Studies on influenza, Joseph Stokes, Jr. (by invitation), Dorothy R. Shaw (by invitation), Athol S. Kenney (by invitation); Discussion of papers d and e by Thomas Francis, Jr.

JANUARY 17—*Ophthalmology.* Instructional Hour—Diseases of the cornea, Bernard Samuels, Edward B. Burchell (by invitation). ¶ Slit Lamp Demonstration, Milton L. Berliner, Wendell L. Hughes, Girolamo Bonaccolto, Gordon M. Bruce. ¶ Reading of the minutes. ¶ Presentation of cases—a] Simple operation for spastic entropion, Sigmund A. Agatson; b] Comparison of operations for paralysis of the external rectus, Brittain F. Payne. ¶ Paper of the evening—Anomalous projection and other visual phenomena associated with strabismus, Frederick H. Verhoeff (by invitation).

JANUARY 18—*Medicine.* Reading of the minutes. ¶ Papers of the evening—a] The present knowledge of vitamin requirement in man, Henry C. Sherman, Mitchill Professor of Chemistry, Columbia University (by invitation); Discussion, R. R. Williams (by invitation), I. Ogden Woodruff; b] Pathological responses to vitamin deficiencies, Gilbert Dalldorf (by invitation); Discussion, C. P. Rhoads. ¶ General discussion.

JANUARY 19—*Genito-Urinary Surgery.* Reading of the minutes. ¶ Presentation of cases—Three cases of tuberculous meningitis following nephrectomy, G. Aubrey Hawes (by invitation). ¶ Paper of the evening—Renal tuberculosis in patients with active pulmonary tuberculosis, Edwin M. Jameson, Saranac Lake (by invitation). ¶ Discussion, Edwin Beer, George F. Cahill, Thomas J. Kirwin.

JANUARY 19—*Otolaryngology.* Reading of the minutes. ¶ Presentation of cases—Cases of cancer of larynx treated by radiotherapy, Maurice Lenz. ¶ Report of cases—a] Salivary fistula, following mastoid operation. Two cured cases, E. B. Bilschick (by invitation); b] Chondroma of the bronchus. Report of two cases, A. J. Cracovaner; c] An unusual case of epithelioma of the nasopharynx, G. E. Bradford (by invitation); d] Multiple myeloma of the temporal bone, E. P. Fowler, Jr. (by invitation); e] Epistaxis from telangiectases, treated by quinine urethane injection, G. H. O'Kane (by invitation); f] Traumatic rupture trachea, George Worcester (by invitation). ¶ Papers of the evening—a] Foci of infection in rheumatoid arthritis, R. L. McCollom (by invitation); b] A new double bronchoscope, G. R. Brighton; c] A critique of the treatment of laryngeal cancer, J. D. Kernan; Discussion by R. E. Buckley, M. Lenz. ¶ General discussion. The cases presented were chiefly from the Service of Prof. John D. Kernan at Presbyterian Hospital, Babies Hospital and Vanderbilt Clinic.

JANUARY 25—*Obstetrics and Gynecology.* Papers of the evening—a] Treatment of pelvic inflammation by iontophoresis of a choline compound, Adolph Jacoby; Discussion, Walter T. Dannreuther, Irving S. Wright, David N. Barrows; b] Management of the third and fourth stages of labor, Morris Leff; Discussion, William E. Caldwell, Alfred C. Beck, William E. Studdiford, John B. Pastore; c] The problem of the after-coming

head, Robert J. Lowrie; Discussion, James P. Hennessy, Claude E. Heaton.

Orthopedic Surgery. Notice—On account of the meeting of the American Academy of Orthopedic Surgeons at Los Angeles this month, no meeting of the Orthopedic Section at the Academy was held.

AFFILIATED SOCIETIES

New York Roentgen Society. The Annual Roentgenological Conference of the Eastern Societies was held in Philadelphia January 28 and 29, and took the place of the regular January meeting of the New York Roentgen Society.

JANUARY 27—*New York Pathological Society in affiliation with The New York Academy of Medicine.* Case Reports—a] Masculinization associated with an ovarian tumor (luteoma vs. hypernephroma), Antonio Rottino; b] Cystic lymphangiectasia of the adrenal, S. Milton Rabson, Edward F. Zimmerman (by invitation); c] Three interesting carcinomas arising in the biliary tract, L. H. Meeker, George Saypol (by invitation); d] Ulceration of peritoneum (chemical?), L. H. Meeker, J. M. Gannon (by invitation); e] Carcinoma (metastatic) and coexisting acute appendicitis with perforation, L. H. Meeker, S. R. Weinberg (by invitation). ¶ Papers of the evening—a] General observations on the serum therapy of infections with streptococcus, Adele E. Sheplar (by invitation), Martha Jane Spence, M.A. (by invitation), Ward J. MacNeal; b] Further observations on bacteriophage action in the presence of blood, Ward J. MacNeal, Margaret A. McRae, B.S. (by invitation), Rudolph A. Colmers (by invitation). ¶ Slide Demonstrations—a] Phagocyted staphylococci in the circulating blood, E. H. Pahl, B.S. (by invitation), Ward J. MacNeal; b] Differentially stained particles within bacteria undergoing lysis by bacteriophage, Ward J. MacNeal, Frances C. Frisbee, A.B. (by invitation). ¶ Executive session—Election of officers.

JANUARY 19—*New York Section of the Society for Experimental Biology and Medicine.* The path of escape of vital dyes from the lymphatics into the tissues, Philip D. McMaster, Robert J. Parsons (by invitation). ¶ Differences in the temperature of the skin and muscles of the lower extremities following various procedures, Mae Friedlander, Samuel Silbert, William Bierman, Norman Laskey (Introduced by Gregory Schwartzman). ¶ The effect of kidney retention and other factors on the excretion of vitamin C after an intravenous dose of cevitamic acid, Irving S. Wright, Elizabeth MacLenathen. ¶ Reversed iontophoresis of histamine from human skin. Its bearing on the histamine theory of the allergic wheal, H. A. Abramson, M. Engel (by invitation), V. Lubkin (by invitation), I. Ochs (by invitation). ¶ The effect of pH on the metamorphosing action of the thyroxine upon tadpoles, S. H. Rosen (Introduced by D. Perla). ¶ The fate of tubercle bacilli in sensitized and in immunized animals, Jules Freund, D. Murray Angevine (by invitation). ¶ The reticuloendothelial system and the concept of the "anti-hormone," Albert S. Gordon (by invitation), William Kleinberg (by invitation), Harry A. Charipper.